DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

[Docket No. FDA–2005–N–0464 (formerly 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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing drug establishment registration and drug listing. These amendments reorganize, modify, and clarify current regulations concerning who must register establishments and list human drugs, human drugs that are also biological products, and animal drugs. The final rule requires electronic submission, unless waived in certain circumstances, of registration and listing information. This rulemaking pertains to finished drug products and to active pharmaceutical ingredients (APIs) alone or together with one or more other ingredients. The final rule describes how and when owners or operators of establishments at which drugs are manufactured or processed must register their establishments with FDA and list the drugs they manufacture or process. In addition, the rule makes certain changes to the National Drug Code (NDC) system. We are taking this action to improve management of drug establishment registration and drug listing requirements and make these processes more efficient and effective for industry and for us. This action also supports implementation of the electronic prescribing provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) and the availability of current drug labeling information through DailyMed, a computerized repository of drug information maintained by the National Library of Medicine.

DATES: This rule is effective on November 29, 2016. See section IV for compliance dates.

FOR FURTHER INFORMATION CONTACT: *For information pertaining to human drug products:* Paul Loebach, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2262, Silver Spring, MD 20993, 301–796–2173.

For information pertaining to human biological drug products or human cells, tissue, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the Public Health Service Act: Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993, 240–402–7911.

For information pertaining to animal drug products: Charise Kasser, Center for Veterinary Medicine (HFV–212), Food and Drug Administration, 7519 Standish Pl., Rm. 2626, Rockville, MD 20855, 240–402–6816; or Isabel Pocurull, Center for Veterinary Medicine (HFV–226), Food and Drug Administration, 7519 Standish Pl., Rm. 2636, Rockville, MD 20855, 240–402–5877.

SUPPLEMENTARY INFORMATION:

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Executive Summary

Purpose of the Regulatory Action

This final rule amends FDA's longstanding regulations governing drug establishment registration and drug listing. The amendments are aimed at modernizing these regulations and improving efficiency and reliability for FDA and drug manufacturers. These amendments also bring FDA's regulations governing drug establishment registration and listing into conformance with section 510 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360) as amended by the Food and Drug Administration Amendments Act (FDAAA) (Pub. L. 110–85) and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112–144).

Since the 1962 Kefauver Harris amendments to the FD&C Act (Pub. L. 87–781), drug manufacturers have been required to register their establishments with FDA annually. Among other things, drug establishment registration identifies establishments for inspection by FDA. In 1973, the FD&C Act was further amended to require each registered establishment to submit a list of drugs it manufactures. FDA's regulations implementing these requirements are found in part 207 (21 CFR part 207) (pertaining to drugs and biological products generally) and part 607 (21 CFR part 607) (pertaining to blood and blood products). Manufacturers of HCT/Ps register and list either under part 207, part 807 (21 CFR 807), or under part 1271 (21 CFR part 1271), issued under authority of the Public Health Service Act (PHS Act), depending on the type of HCT/P product they manufacture.

The amendments to parts 207 and 607 adopted by this final rule modernize those regulations and bring them into conformance with section 510 of the FD&C Act following recent amendments.

Summary of the Major Provisions of the Regulatory Action

This final rule requires electronic submission, unless waived in certain circumstances, of drug establishment registration and listing information. The electronic submission requirement is consistent with FDAAA and with current practice.

The rule makes clear that the establishment registration and listing obligation rests with persons who manufacture, repack, relabel, or salvage drug products. The rule does not require persons who act only as private label distributors of drug products to register establishments or list drugs, but allows them to submit drug listing information as agents acting on behalf of persons who manufacture, repack, relabel, or salvage drug products. The amendments make several adjustments to the timing and substance of the submission of information to register a drug establishment and list drugs manufactured, repacked, relabeled, or salvaged at the establishment. The amendments also update longstanding regulatory provisions governing FDA disclosure of drug registration and listing information, stating that with certain exceptions, establishment registration and drug listing information is generally available for public disclosure.

This final rule does not include certain aspects of the proposed rule that were opposed by many who submitted comments. Features of the proposed rule that have not been finalized include most significantly: (1) A requirement that FDA, not registrants, develop national drug codes (NDCs) for assignment to listed drugs and (2) a requirement that the NDC appear in human-readable form on the label of each listed drug and provisions that would have defined the appropriate NDC for that purpose. As discussed in section III, revisions to the FD&C Act require human-readable NDCs on certain drug labels.

Benefits and Costs

All incremental costs from the final rule are one-time costs, except for registrants' annually recurring costs of certifying no change to listings upon annual registration for part 207 registrants. We estimate one-time total costs of $59.7 million and recurring costs of $0.5 million. These costs represent total annualized costs of $9 million when calculated at a 7-percent discount rate over 10 years, and $7.5 million when calculated using a 3-percent discount rate. The largest cost elements will be for registrants reading and understanding the final rule and making changes to their standard operating procedures.

SUMMARY OF TOTAL INCREMENTAL COST OF THE FINAL RULE

[$ millions]

Affected firms	One-time costs	Recurring costs (annual)	Total costs annualized at 7%	Total costs annualized at 3%
Drugs and biological products (part 207)	$48.9	$0.5	$7.5	$6.2
Human blood products (part 607)	5.1	N/A	0.7	0.6
Human cell and tissue products (part 1271)	5.7	N/A	0.8	0.7
Total [1]	59.7	0.5	9.0	7.5

[1] Total costs are annualized over a 10-year period. Recurring costs include only annual time costs of certifying that there are no changes to listings; these costs are unique to part 207. All estimates reflect rounded 2014 dollars.

By codifying the statutory requirements of FDAAA and FDASIA, the final rule clarifies and completes the modernization of our electronic registration and listing systems. Thus, the final rule will improve management of the establishment registration and drug listing requirements and make these processes more efficient and effective for industry and for us. The final rule also supports implementation of the electronic prescribing provisions of the MMA and the availability of current drug labeling information through DailyMed, a computerized repository of drug information maintained by the National Library of Medicine.

I. Background

In the **Federal Register** of August 29, 2006 (71 FR 51276), FDA proposed to amend its regulations governing drug establishment registration and drug listing in part 207 (proposed rule). The proposed rule included ancillary amendments to parts 20, 201, 314, 514, 515, 601, 607, and 1271 (21 CFR parts 20, 201, 314, 514, 515, 601, 607, and 1271). These amendments reorganize, modify, and clarify current regulations concerning who must register establishments and list human drugs, human drugs that are also biological products, and animal drugs. The proposed rule and the final rule both specify that drug establishment registration and drug listing information generally must be submitted to FDA electronically.

After the proposed rule was published, FDAAA was adopted into law. FDAAA amended section 510(p) of the FD&C Act to require electronic submission of drug establishment registration and listing information, unless FDA waives the electronic submission requirement in individual cases. In June 2009, FDA announced publication of a guidance for industry on ''Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing'' consistent with FDAAA (74 FR 26248, June 1, 2009, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) (the electronic registration and listing guidance). This guidance applied to establishment registration and listing required under part 207. It did not apply to information required solely under part 607 (blood and blood products), part 807 (devices), or part 1271 (human cells, tissues, and cellular and tissue-based products). FDA generally stopped receiving drug establishment registration and listing information required under part 207 submitted on paper in June 2009, allowing paper submissions only if supported by a waiver from the electronic submission requirement in individual cases. This final rule is consistent with the electronic submission provisions of FDAAA.

FDASIA made further amendments to section 510 of the FD&C Act in 2012 to specify that:

- Annual registration of establishments takes place during the period beginning on October 1 and ending on December 31.
- The information registrants supply for annual registration includes a Unique Facility Identifier (UFI) for the establishment and includes a point-of-contact email address.

This final rule includes changes to the proposed rule consistent with these statutory provisions. The electronic registration and listing guidance stated that FDA intended to use the Data Universal Numbering System (DUNS) number, assigned and managed by Dun

& Bradstreet, as a registration number. In 2014, FDA announced publication of a guidance for industry on ''Specifications of the Unique Facility Identifier (UFI) System for Drug Establishment Registration,'' (79 FR 65977, November 6, 2014, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)), in which FDA specified the DUNS number as the preferred UFI.

II. Overview of the Final Rule Including Changes to the Proposed Rule

A. Overview

The final rule adopts significant amendments to FDA's regulations governing drug registration and listing. It modernizes these regulations to require electronic submission of drug establishment registration and listing information and to otherwise match current statutory requirements and FDA's information needs.

The final rule:

- Makes minor technical amendments to §§ 20.100, 20.116, and 201.1 (updating citations to regulations in part 207).
- Removes from § 201.2 a statement about the manner in which NDCs are displayed on drug labels.
- Amends § 201.25 to allow an FDA Center Director to approve an additional bar code standard or format.
- Revises part 207 significantly.
- Amends § 314.81(b)(3)(iv) (requiring holders of approved new drug applications (NDAs) to report the withdrawal of approved drug products from sale) to make it consistent with part 207.
- Makes a minor conforming amendment to § 314.125(b)(11) (stating FDA may refuse to approve a new drug 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 FD&C Act and part 207).
- Adds new § 514.111(a)(12) stating FDA will refuse to approve a new animal drug application if the drug will be produced in whole or in part in an establishment that is not registered and is not exempt from registration under section 510 of the FD&C Act and part 207.
- Makes a minor technical amendment to § 515.10(b)(8), updating a reference to the regulations in part 207.
- Adds new § 601.2(f) requiring holders of biologics license applications (BLAs) to report to FDA electronically in accordance with part 207 the withdrawal from sale of licensed biological products.
- Amends part 607 (ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS) consistent with the amendments to part 207, to require electronic submission of establishment registration and listing information.
- Amends part 1271 (HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE–BASED PRODUCTS) to require electronic submission of establishment registration and listing information, to state that manufacturers of HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act (42 U.S.C. 262) or under the FD&C Act are subject to registration and listing under part 207 or part 807, and to make other revisions consistent with the amendments to part 207.

B. Changes to the Proposed Rule

The final rule has been revised in response to comments received on the proposed rule. Our responses are discussed in section III. The final rule also includes several minor editorial revisions. The final rule makes the changes summarized in table 1.

TABLE 1—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE

21 CFR Section in final rule	Description of change from proposed rule
201.2	Labeling. • Does not include proposed revisions to § 201.2 requiring human-readable NDCs on labels.
201.25	Bar code label requirements. • Revises § 201.25(c)(1) to accommodate alternatively formatted NDCs in bar codes. • Does not include other proposed amendments to § 201.25.
207.1	Definitions. • Includes definitions for the terms ''finished drug product,'' ''unfinished drug product,'' ''bulk drug substance,'' ''private label distribution,'' ''registrant,'' and ''outsourcing facility'' not included in the proposed rule. • States that the definitions and interpretations of terms in sections 201 (21 U.S.C. 321) and 510 of the FD&C Act apply to the terms used in part 207, if not otherwise defined in § 207.1. • Includes revised definitions of the terms ''active pharmaceutical ingredient,'' ''commercial distribution,'' ''content of labeling,'' ''importer,'' ''manufacture,'' ''private label distributor,'' ''relabel,'' ''repack,'' and ''representative sampling of any other labeling''.
207.9	Who does this part cover? • Clarifies that private label distributors are subject to part 207 (because they must have labeler codes). • States that all drugs regulated under a BLA, except human blood or blood products regulated under part 607, are subject to part 207 and clarifies that for this purpose certain products are not included in the phrase ''human whole blood and blood products''. • States that HCT/Ps regulated as drugs under section 505 of the FD&C Act (21 U.S.C. 355) or section 351 of the PHS Act are subject to part 207.
207.13	Who is exempt from the registration and listing requirements? • Generally exempts from registration and listing individuals or establishments engaged solely in recovering cells or tissues to become components of a biological product at a registered establishment. • Eliminates a reference to salvagers of inactive ingredients because salvaging, as defined, is performed only on finished drug products. • Revises § 207.13 to clarify the applicability of part 207 to medicated feeds. • Revises § 207.13 to remove a reference to HCT/Ps made unnecessary by revisions to § 207.9. • Adds an exemption for outsourcing facilities registered under section 503B of the FD&C Act (21 U.S.C. 353b) so as to avoid duplicative registration for those entities. • Retains the previous establishment registration exemptions for certain drugs entering foreign trade zones and certain drugs imported for export.
207.17	Who must register?

TABLE 1—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE—Continued

21 CFR Section in final rule	Description of change from proposed rule
	• Revises § 207.17(b) to state that FDA will accept establishment registration or listing information submitted by a private label distributor if it is acting as an authorized agent for an establishment that manufactures, repacks, relabels, or salvages drugs.
207.25	What information is required for registration? • Revises proposed § 207.25 to include the UFI required as part of establishment registration under FDASIA.
207.29	What are the requirements for reviewing and updating registration information? • Revises § 207.29 to specify that registrants must review and update registration information between October 1 and December 31 each year, consistent with FDASIA.
207.33	What is the National Drug Code (NDC), how is it assigned, and what are its requirements? • Allows for 10- or 11-digit NDCs, consistent with a longstanding statement in § 207.35(b)(2)(i), as it read prior to this final rule, that FDA will expand the NDC labeler code from 5 to 6 numeric characters when the available 5-character code combinations are exhausted. • States that registrants will propose NDCs for assignment by FDA. • Includes formatting requirements for registrants to follow when formulating their own proposed NDCs. • Allows for alternatively formatted NDCs for certain HCT/Ps. • Explains how a labeler code can be obtained. • Allows registrants to reserve an NDC for a drug product under development. • Eliminates proposed § 207.33(c). (What information must a manufacturer submit before we will assign an NDC number to a drug?) • Adds some information elements described in proposed § 207.33(c) to the drug listing information now described in § 207.49 (Added to the listing information required under § 207.49 are the names of inactive ingredients in the listed drug and in the case of an unfinished drug, the number assigned to the Drug Master File or Veterinary Master File, if any, that describes the manufacture of the drug). • The option to submit an approved U.S. application number instead of a list of inactive ingredients for a finished drug product (as proposed in § 207.33(c)) is not retained in § 207.49 of this final rule.
207.35	What changes require a new NDC? • Introduces new § 207.35 to more clearly explain what changes to drugs require a new NDC and does not include inactive ingredient changes in this section.
207.37	What restrictions pertain to the use of the NDC? • Revises § 207.37 to state that a product may be deemed to be misbranded if an NDC is used improperly.
207.41	Who must list drugs and what drugs must they list? • Revises § 207.41 to clarify the manner in which human drugs that are manufactured, repacked, or relabeled for private label distribution are listed.
207.45	When, after initial registration of an establishment, must drug listing information be submitted? • Revises § 207.45 to state that drug listing must take place no later than 3 calendar days after initial registration of an establishment, rather than "at the time of" initial registration.
207.49	What listing information must a registrant submit for a drug it manufactures? • Revises § 207.49 to reflect that registrants will propose their own NDCs under the final rule. • Eliminates the requirement of proposed §§ 207.49(f), 207.53(c), and 207.54(b)(4) (which would have required foreign establishments to identify importers when listing drugs they manufacture, repack, relabel, or salvage). (This is now reported only as establishment registration information for foreign establishments.). • Expands the language of proposed § 207.49(d) (now § 207.49(a)(11)) to make clear that a registrant's own establishment(s) must be identified in drug listing information as well as other establishments involved in the production of unfinished drugs received by the registrant and to require identification of all such establishments using their UFIs. • Removes from proposed § 207.49 the option to provide an approved U.S. application number instead of labeling. • Revises § 207.49 (also §§ 207.1 and 207.53) to categorize certain drug products according to whether they are subject to sections 505 or 512 of the FD&C Act (21 U.S.C. 355 or 360b) or section 351 of the PHS Act, rather than whether registrants regard them as subject to those provisions. • Adds §§ 207.49(a)(15)(iv) and 207.53(d)(4) to require the submission of labels for listed drugs not elsewhere described in §§ 207.49(a)(14) and 207.53(d). • Clarifies in new §§ 207.49(a)(15) and 207.53(f) the information a registrant must submit when listing a human drug manufactured for private label distribution. • Adds § 207.49(b) to describe drug listing information that is requested of registrants but not required. • Adds § 207.49(a)(2) so that drug listing information includes package size and type.
207.53	What listing information must a registrant submit for a drug that it repacks or relabels? • Shifts from proposed § 207.33(d)(1)(iii) to new § 207.53(b) the requirement that for a repacked or relabeled drug, registrants identify the NDC assigned to the finished drug received by the registrant for repacking or relabeling and exempts repackaged medical gases from this requirement. • Requires identification of establishments where repacking, or relabeling is performed based on their UFIs rather than by their registration numbers. • Clarifies that all current labeling (new labeling) for a repacked or relabeled drug must be submitted, not only the changed labeling. • Specifies that for animal drugs subject to section 512 of the FD&C Act, all current *labeling* is submitted, whereas a copy of the current *label,* and other information, is submitted for other animal drugs.
207.54	What listing information must a registrant submit for a drug that it salvages? • Requires identification of establishments where salvaging is performed by their UFIs rather than by their registration numbers. • Deletes references to salvaged drugs distributed by private label distributors.
207.57	What information must registrants submit when updating listing information and when? • Revises proposed § 207.57 to improve clarity and to delete the proposed requirement that registrants routinely update information provided under § 207.55.

TABLE 1—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE—Continued

21 CFR Section in final rule	Description of change from proposed rule
	• Allows registrants to submit a blanket ''no changes'' certification applicable to listing information they have previously submitted electronically, rather than making product-by-product ''no changes'' certifications for individual listed drugs.
207.61	How is registration and listing information provided to FDA? • Revises § 207.61 to improve clarity, to state that we may periodically issue guidance on electronic registration and listing, and to clarify that when foreign language labeling is used under § 201.15(c), the content of labeling must be submitted in that foreign language along with an accurate English translation. • Removes the option to submit advertisements and certain labeling in paper format, consistent with the electronic submission requirement of section 510(p) of the FD&C Act, as amended by FDAAA.
207.65	How can a waiver of the electronic submission requirement be obtained? • Clarifies that requests for waivers of the electronic submission requirement cannot be relied upon until FDA grants them. • States more broadly the conditions under which FDA will grant waiver requests. • Specifies that waiver requests must be submitted in writing and must state reasons why electronic submission is not reasonable for the registrant. • States that FDA will specify terms of waivers and may limit their duration.
207.69	What are the requirements for an official contact and a United States agent? • Revises proposed § 207.69 to state that designated official contacts and United States agents are both responsible for reviewing, disseminating, routing, and responding to all communications from FDA, including emergency communications.
207.77	What legal status is conferred by registration and listing? • Includes minor revisions to improve clarity and mentions the UFI that will be used to identify establishments.
207.81	What registration and listing information will FDA make available for public disclosure? • Reorganizes § 207.81 so that registration and listing information that will be disclosed is described in paragraph (a), and exceptions are described in paragraphs (b) and (c). • Categorizes updated drug listing information submitted under § 207.57 as generally disclosable. • Adds § 207.81(b)(2) to make explicit that FDA will generally not disclose the names of inactive ingredients in listed drug products if the registrant makes a valid assertion of confidentiality. • Categorizes the information submitted to reserve an NDC under new § 207.33(d)(3) as generally not disclosable. • Categorizes the identities of the establishments involved in manufacturing, repacking, relabeling, or salvaging listed drugs as generally not disclosable. • Categorizes as generally not disclosable the NDC assigned to an unfinished drug received by a registrant for use in the manufacture of a listed drug reported under § 207.49(a)(12) (*i.e.*, the association between the unfinished drug and the listed drug is generally not disclosable). • No longer categorizes the NDC assigned to a drug immediately before it is received by a registrant for salvaging as generally not disclosable (because the NDC assigned to a drug does not change when a drug is merely salvaged and not also repackaged or relabeled).
314.81	Other postmarketing reports (reporting the discontinuation of a drug that is the subject of an approved NDA). • Renumbers proposed § 314.81(b)(3)(iii) as § 314.81(b)(3)(iv) and revises this section to provide for electronic or written submissions in certain circumstances, under both paragraphs (a) and (b).
601.2(f)	Applications for biologics licenses (reporting the discontinuation of a drug that is licensed under a BLA). • Revises proposed § 601.2(f) to reference the electronic submission requirement of § 207.61 and the waiver provision of § 207.65 and to clarify that the date on which the product is expected to be no longer in commercial distribution must be reported rather than the ''date of withdrawal from sale''.
607.1	Scope (Establishment registration and product listing for manufacturers of human blood and blood products.) • Adds a new scope provision (§ 607.1) to part 607 for clarity.
607.3	Definitions (Establishment registration and listing for blood and blood products). • Adds a definition of ''foreign''. • Revises the proposed definition of ''importer''.
607.22	How to register blood product establishments and list blood products. • Revises proposed § 607.22 to remove references to Form FDA 2830 and to state that blood product establishment registration and blood product listing must be transmitted to FDA electronically through the Blood Establishment Registration and Product Listing system, unless FDA waives the electronic submission requirement in individual cases.
607.25	Information required for establishment registration and blood product listing. • Removes references to Form FDA 2830. • Requires submission of a UFI when registering blood and blood product establishments along with a registration number if previously assigned by FDA. • Adds the UFI of the parent establishment to blood product listing information required under § 607.25(b)(3).
607.26	Amendments to establishment registration. • Revises § 607.26 regarding amendments to establishment registration to reference the Blood Establishment Registration and Listing System in place of Form FDA 2830. • Clarifies that 5 days refers to 5 calendar days in this section.
607.30	Updating blood product listing information. • Revises § 607.30 regarding updates to blood product listing information to reference the Blood Establishment Registration and Listing System in place of Form FDA 2830.
607.37	Public disclosure of establishment registration and blood product listing information. • Revises § 607.37 to remove references to Form FDA 2830. • Structures § 607.37 in a way that matches § 207.81 (public disclosure of drug registration and listing information).
607.40	Establishment registration and blood product listing requirements for foreign blood product establishments. • Retains the exemptions applicable to foreign trade zones and products imported under section 801(d)(4) of the FD&C Act (21 U.S.C. 381(d)(4)).

TABLE 1—SUBSTANTIVE CHANGES FROM THE PROPOSED RULE TO THE FINAL RULE—Continued

21 CFR Section in final rule	Description of change from proposed rule
	• Revises proposed § 607.40 to state more broadly the circumstances under which FDA will waive the electronic submission requirement for foreign blood product establishments.
607.80	Applicability of part 607 to licensed devices.
	• Adds a new § 607.80 clarifying the applicability of part 607 to certain licensed devices.
1271.1	What are the purpose and scope of this part? (HCT/Ps)
	• Adds the word ''electronic'' in place of ''unified'' in § 1271.1.
1271.3	How does FDA define important terms in this part?
	• Revises the definition of ''importer'' in proposed § 1271.3(mm) to include ''at the time of entry''.
1271.20	If my HCT/Ps do not meet the criteria in § 1271.10, and I do not qualify for any of the exceptions, what regulations apply?
	• Adds a further amendment to § 1271.20 to indicate that subpart B of part 1271 (procedures for registration and listing) does not apply to HCT/Ps that do not meet the criteria set out in § 1271.10(a). (In other words, HCT/Ps not regulated solely under section 361 of the PHS Act are subject to registration and listing under part 207 or part 807 rather than part 1271.)
1271.25	What information is required for establishment registration and HCT/P listing?
	• Removes from proposed § 1271.25(a)(6) the requirement that each foreign HCT/P establishment designate only one United States agent.
	• Removes a reference to Form FDA 3356 in proposed § 1271.25(c)(4).
	• Revises proposed § 1271.25(d) to clarify that it pertains to HCT/Ps regulated under BLAs and to state that establishment registration and listing information for such products must be submitted in accordance with the electronic submission requirements of part 207, subpart E.

This final rule does not include the proposed amendments to §§ 330.1, 610.60, and 610.61, all of which dealt with NDCs on labels. This final rule also does not include the proposed minor amendment to § 1271.37 (regarding public disclosure of HCT/P establishment registration and listing information) in light of the technical amendments adopted on April 3, 2015 (80 FR 18087).

Some changes from the proposed rule not addressed in section III (Comments on the Proposed Rule) are addressed in the following paragraphs.

Active pharmaceutical ingredient: To prevent confusion, we proposed to replace the term ''bulk drug substance'' with the more descriptive term ''active pharmaceutical ingredient.'' This change is retained in the final rule. Sections 503A(b)(1)(A) and 503B(a)(2) of the FD&C Act (21 U.S.C. 353a(b)(1)(A) and 353b(a)(2)), however, refer specifically to the definition of ''bulk drug substance'' within part 207. To ensure conformity with the FD&C Act, both ''bulk drug substance'' and ''active pharmaceutical ingredient'' are defined in § 207.1 of the final rule. As intended by the proposed rule, ''active pharmaceutical ingredient'' will have the same meaning as ''bulk drug substance.''

Salvage: In this final rule, the term ''salvage'' is defined to mean the act of segregating out those finished 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 and includes applying manufacturing controls such as those required by current good manufacturing practice in parts 210 and 211 (21 CFR parts 210 and 211). Substantively, this matches the definition of ''drug product salvaging'' included in the proposed rule, but the words have been rearranged for greater clarity. This final rule also includes a definition for the term ''salvager.''

Establishment registration number and Unique Facility Identifier: We proposed to define the term ''establishment registration number'' in § 207.1 to mean ''the number assigned by FDA to the establishment during the establishment registration process required in this part.'' The final rule changes the definition of ''establishment registration number'' slightly to state that the number is assigned ''after'' the registration process, rather than ''during.''

The establishment registration number identifies establishments for inspection by FDA. Historically, an establishment registration number is assigned to each establishment of each manufacturer, repacker, relabeler, or salvager after the initial registration, when such activities begin. In the preamble to the proposed rule, we explained that ''[c]urrently, 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'' (71 FR 51276 at 51288).

After the proposed rule was published, FDASIA amended section 510 of the FD&C Act to require persons subject to the drug establishment registration requirement to submit a UFI. In the electronic registration and listing guidance, FDA stated that it intended to use the DUNS number, assigned and managed by Dun & Bradstreet, as a registration number. To implement the UFI provision of FDASIA, FDA also issued guidance in 2014 that specified the DUNS number as the preferred UFI.[1]

Under the final rule, the establishment registration number and the UFI are two distinct numbers. For now, FDA will continue to assign an FEI as the establishment registration number after an establishment is registered for the first time. The final rule requires registrants to submit the establishment registration number (currently the FEI), ''if previously assigned by FDA,'' under § 207.25. Someone registering an establishment for the first time is not expected to have a registration number for the establishment. Such a registrant is required to submit its registration number at the time of the first annual review and update of registration information under § 207.29(b) of this final rule and is encouraged to submit the registration number sooner, as soon as it is received from FDA. The establishment registration number does not need to be submitted at the time of each annual registration update under § 207.29 unless the establishment registration number has changed. Likewise, the UFI, currently specified as

[1] See the guidance for industry ''Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration,'' November 2014, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs).

the DUNS number, must be submitted when registering an establishment for the first time under § 207.25. The UFI does not need to be submitted at the time of each annual registration update under § 207.29 unless the UFI has changed.

Bar code label requirements (§ 201.25): As explained in section III, this final rule does not include two proposed amendments to § 201.25. It does, however, include a minor new amendment to § 201.25. To accommodate the possibility of alternatively formatted NDCs in bar codes, § 201.25 is amended in this final rule to allow FDA's Center Directors to approve additional standards or formats for bar codes.

Submission of approved U.S. application number instead of inactive ingredients (§ 207.33(c)(2)): Information registrants would have submitted under § 207.33(c) of the proposed rule to obtain an NDC has been shifted to drug listing information required under § 207.49 of this final rule. Under § 207.49(a)(5) of this final rule, a registrant must provide the name of each inactive ingredient in a listed drug it manufactures. The option to submit an approved application number instead of a list of inactive ingredients is not retained in the final rule because FDA is not currently able to pull inactive ingredient information from approved applications to our drug listing systems.

III. Comments on the Proposed Rule

In the **Federal Register** of October 31, 2006 (71 FR 63726), FDA announced an extension of the comment period for this rulemaking and a public meeting to discuss the proposed changes to the NDC system presented in the proposed rule. The public meeting was held on December 11, 2006. In the **Federal Register** of February 8, 2007 (72 FR 5944), FDA announced a reopening of the comment period because technical problems prevented some persons from submitting comments electronically on the last day of the previous comment period. The Agency received numerous comments, including oral presentations made at the December 2006 public meeting and approximately 200 written comments placed in the docket. Comments were received from prescription and nonprescription drug manufacturers and related companies, trade associations representing drug manufacturers and other interested parties, academic institutions, and professional associations.

The docket for this rulemaking, Docket No. FDA–2005–N–0464, was also used to collect comments on FDA's draft guidance for industry entitled ''Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing'' (74 FR 26248). In this final rule, we are responding to comments that pertain to the rulemaking, *i.e.,* comments that relate to the changes in regulations proposed on August 29, 2006.

To make it easier to identify comments and our responses, the word ''Comment,'' in parentheses, appears before the comment's description, and the word ''Response,'' in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

A. Labeling (§§ 201.2 and 201.25)

The proposed rule included amendments to § 201.2 that would have required drugs subject to the listing requirement of part 207 to have labels that bear the appropriate NDC in human-readable form. As discussed in this document, this final rule does not include the proposed amendments that would have made human-readable NDCs mandatory on drug labels.

Section 201.2 currently states that NDCs are ''requested but not required'' to appear on all drug labels. Section 201.25 currently requires bar codes on prescription human drug labels with certain exceptions and on certain nonprescription human drug labels. Section 201.25(c) currently specifies that each bar code must contain, at a minimum, the appropriate NDC.

Sections 201.2 and 201.25 currently do not specify which NDC should appear on labels and in bar codes apart from referring to it as ''the appropriate'' NDC (§ 201.25(c)). This implies that the NDC appearing on a drug's label match an NDC under which the drug is appropriately listed under part 207.

1. NDC Numbers (§ 201.2)

Pharmacists and health care providers use NDCs currently appearing on drug labels in a variety of ways, including to help prevent medication errors and to process prescription drug reimbursement claims. We believe there is currently a high level of cooperation with FDA's request in § 201.2 that NDCs appear in human-readable form on labels, as drug manufacturers recognize the importance of this information.

In addition to making human-readable NDCs on drug labels mandatory, the proposed rule would have specified which NDC must appear on labels. Specifically, proposed § 201.2(b) sought to define the appropriate NDC for this purpose as being that of the last manufacturer, repacker, relabeler, or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer.

(Comment 1) Several comments recognized the importance of having NDCs in human-readable form on labels, but many objected to FDA's proposed provisions defining the appropriate NDC in proposed § 201.2(b). In particular, certain repackers objected to the proposed requirement that a repacker's NDC, rather than that of the original manufacturer, appear on the labels of repackaged drug products.

(Response) This final rule does not include the proposed amendments to § 201.2 that would have made human-readable NDCs mandatory on drug labels. It includes only a conforming amendment to that section (replacing the reference to § 207.3(b)(3) with an updated reference to new § 207.1).

The Drug Quality and Security Act (DQSA) (Pub. L. 113–54) of 2013 includes as Title II the Drug Supply Chain Security Act (DSCSA). The DSCSA requires drug manufacturers and repackagers (as defined in sections 581(10) and 581(16) of the FD&C Act, respectively) to affix or imprint a *product identifier* on packages for certain prescription drugs for human use. Under section 581(14) of the FD&C Act, a ''product identifier'' is a standardized graphic that includes, in both human-readable form and on a machine-readable data carrier, the ''standardized numerical identifier,'' lot number, and expiration date of the product. The NDC is one component of the standardized numerical identifier. FDA has determined that because the DSCSA requires the inclusion of NDCs on certain prescription drug labels (as part of a product identifier), it is unnecessary to include the proposed amendments to § 201.2 in this final rule.

Our determination that the proposed amendments to § 201.2 should not be finalized renders moot many comments concerning identification of the appropriate NDC for labeling purposes, along with placement and formatting issues. Therefore, we do not respond to those comments.

The DSCSA does not require manufacturers or repackagers to affix or imprint product identifiers on nonprescription human drug products or on animal drugs. Therefore, we will maintain the status quo for those drug products, meaning FDA will continue to request that NDCs in human-readable

form appear on all drug labels and in all drug labeling, as indicated in § 201.2. We may revisit a regulatory requirement that human-readable NDCs appear on the labels of nonprescription human drug products and animal drugs in the future.

2. Bar Code Label Requirements (§ 201.25)

Section 201.25 currently requires that a human drug product's NDC be included in its bar code. We proposed to amend § 201.25 in two minor ways: (1) To add a cross-reference to proposed new § 201.2(b), which would have described the ''appropriate NDC'' for labeling purposes and (2) to add new § 201.25(e) stating that a bar code may be displayed on certain drug product labels voluntarily but only if it meets the requirements of § 201.25(c). Neither proposed amendment to § 201.25 is retained in the final rule.

(Comment 2) The Animal Health Institute expressed concern that proposed § 201.25(e) would unreasonably burden its members who, although they are not currently required by § 201.25 to place bar codes on animal drug labels (because it applies to human drugs), may do so for logistical reasons. They asked that the animal health industry be exempt from the requirement to include an NDC in any bar codes appearing on animal drug labels. Similar comments were received from manufacturers of allergenic extracts. Allergenic extracts are currently exempt from the bar code requirement (see § 201.25(b)(1)(i)(B)). Commenters explained that manufacturers of allergenic extracts may place bar codes on their labels for inventory, warehousing, and other logistical purposes. They objected to proposed § 201.25(e) to the extent that it would require such bar codes to include NDCs.

(Response) FDA has not retained proposed § 201.25(e) in this final rule.

(Comment 3) A group of comments asserted that 11-digit NDCs cannot be encoded into a bar code that meets European Article Number/Uniform Code Council or Health Industry Business Communications Council standards, as required by current § 201.25(c). Another comment urged FDA to remove the NDC from bar codes.

(Response) This final rule acknowledges that 10-digit NDCs will be exhausted at some point in the future as a mathematical inevitability. As discussed in our response to Comment 52, this final rule reduces the number of occasions when a change to a drug requires a new NDC under § 207.35. This final rule also amends § 201.25 to allow FDA's Center Directors to approve additional bar code standards and formats.

As discussed in response to Comment 1, the DSCSA requires the inclusion of product identifiers on prescription human drug labels and defines ''product identifier'' to mean a standardized graphic that includes, in both human-readable form and on a machine-readable data carrier the standardized numerical identifier, lot number, and expiration date of the product. The standardized numerical identifier, a component of the product identifier, is comprised of the NDC and a serial number.

FDA continues to recognize the importance of NDCs on drug labels in both machine-readable and human-readable form. We remind manufacturers of the current requirement in § 201.25 that bar codes on human drug labels include the appropriate NDC, and we encourage manufacturers to continue to provide the NDC in human-readable form on drug labels where not required by the DSCSA.

B. General Information (Part 207, Subpart A)

1. What definitions and interpretations of terms apply to this part? (§ 207.1)

The proposed rule included a set of terms and definitions in §§ 207.1, 607.3, and 1271.3. These definitions are retained in the final rule with several modifications. Additionally, the final rule includes definitions for the terms ''finished drug product,'' ''unfinished drug product,'' ''bulk drug substance,'' ''outsourcing facility,'' ''private label distribution,'' and ''registrant'' in § 207.1 and a definition of ''foreign'' in § 607.3.

a. Commercial distribution. In the proposed rule, the definition of ''commercial distribution'' excluded ''the internal or interplant transfer of an active pharmaceutical ingredient between registered establishments within the same parent, subsidiary, and/or affiliate company.''

In the final rule, the definition does not include the phrase ''an active pharmaceutical ingredient'' so that internal or interplant transfers between such registered establishments are not treated as commercial distribution under part 207, whether the transfer involves active pharmaceutical ingredients, other unfinished drug products, or finished drug products.

(Comment 4) A comment suggested that the definition of ''commercial distribution'' be revised to exclude transfers between a registered establishment and a marketing authorization holder when the two are in a contractual relationship. Otherwise, this comment argued, products marketed by private label distributors who employ contract manufacturers are held to a higher burden of documentation than products manufactured and distributed by the same entity.

(Response) We disagree with the suggestion that a transfer of drugs from a contract manufacturer to another contracting party should not qualify as commercial distribution. Such an exemption would interfere with FDA's ability to track drugs and establishments for inspection. However, by revising the definition of ''commercial distribution'' to exclude internal or interplant transfers of drugs, including active pharmaceutical ingredients, other unfinished drugs, and finished drug products, between registered establishments under common ownership and control, we have reduced the drug listing burden generally. This exclusion accommodates the common practices of specialized manufacturing at different registered establishments under common ownership and control. This practice often results in multiple internal and interplant transfers of these materials prior to marketing, which we do not consider commercial distribution for registration and listing purposes.

b. Content of labeling. The proposed rule included a multipart definition for the term ''content of labeling'' with separate provisions applicable to:

- Human prescription drugs that the manufacturer regards as subject to section 505 of the FD&C Act or section 351 of the PHS Act, *i.e.,* subject to premarket approval from FDA;
- Human prescription drugs that the manufacturer regards as not subject to section 505 of the FD&C Act or section 351 of the PHS Act;
- Human nonprescription drugs; and
- Animal drugs.

The term ''content of labeling'' was used in the proposed rule to describe some, but not all, labeling that must be submitted with drug listing information. For example, proposed § 207.49(g)(2)(i) stated that listing information for certain human over-the-counter (OTC) drugs must include ''all current labeling . . . including the content of labeling.'' Content of labeling is defined in a very similar way in the final rule with deletion of the phrase ''that the manufacturer regards as'' and the addition of a reference to the labeling requirements for veterinary drugs in 21 CFR part 201.

We removed the language ''that the manufacturer regards as subject to section 505 [or 512] of the FD&C Act or section 351 of the PHS Act'' and added in its place language that refers to drugs as being either subject or not subject to those provisions. We made this change after determining that the manner in which content of labeling is defined should not depend on a manufacturer's subjective understanding or intent with respect to sections 505 or 512 of the FD&C Act or section 351 of the PHS Act.

The revised definition includes, among others, the category ''human prescription drugs that are not subject to section 505 of the FD&C Act or section 351 of the PHS Act.'' We have retained this construction even though FDA considers it unlikely that any currently marketed human prescription drug product is grandfathered or is otherwise not a new drug subject to those provisions. However, the Agency recognizes that the existence of such drugs is at least theoretically possible. No part of this final rule is a finding as to the legal status of any particular drug product.

Regarding animal drugs, in part four of the definition of ''content of labeling'' and in other places throughout this final rule, the phrase ''subject to section 512'' means, for purposes of this final rule, drugs meeting the definition of ''new animal drug'' as that term is defined in section 201(v) of the FD&C Act, and which therefore are subject to some or all of the provisions relating to new animal drugs found in section 512 of the FD&C Act. This term includes not only new animal drugs that are approved under section 512 but also new animal drugs that are conditionally approved under section 571 of the FD&C Act (21 U.S.C. 360ccc) or indexed under section 572 of the FD&C Act (21 U.S.C. 360ccc–1). The phrase ''all other animal drugs'' as used in provisions of this final rule at §§ 207.49(a)(15)(iii) and 207.53(d)(3) describing the labeling registrants must provide as part of the listing for an animal drug, refers to animal drugs that do not meet the definition of new animal drug found in section 201(v) of the FD&C Act (*e.g.,* grandfathered animal drugs). Although the Agency recognizes that the existence of such animal drugs is theoretically possible, we believe it is unlikely that any currently marketed animal drug product is grandfathered or otherwise not a ''new animal drug'' subject to section 512 of the FD&C Act.

(Comment 5) Commenters asked FDA to clarify how content of labeling differs from package inserts and final printed labeling.

(Response) A prescription human drug product's FDA-approved labeling is sometimes referred to as a ''package insert'' or as ''professional labeling.'' In defining the term ''content of labeling,'' for human drugs, we use the phrase ''prescription drug labeling'' (instead of ''package insert'' or ''professional labeling'') to mean FDA-approved labeling for prescription drug products described in §§ 201.56, 201.57, and 201.80. For human prescription drugs that are subject to section 505 of the FD&C Act or section 351 of the PHS Act, content of labeling is defined as the content of the prescription drug labeling. For human OTC drugs, content of labeling is not defined in these terms; it includes ''all text, tables, and figures including the drug facts labeling required by § 201.66.'' For animal drugs, ''content of labeling'' is defined to mean labeling that accompanies the drug that is necessary to enable safe and proper administration of the drug. This would generally include package inserts and final printed labeling. Sections 207.49 and 207.53 require submission of labeling with drug listing information. In most cases, all current labeling must be submitted, including the content of labeling.

(Comment 6) A comment stated that FDA should more clearly delineate between the terms ''label'' and ''labeling'' throughout the rulemaking, rather than using the term ''labeling'' to refer to both. This comment pointed out that the proposed rule's definition of content of labeling for human OTC drugs referred to ''labeling required by § 201.66,'' but § 201.66 pertains to information appearing on the ''outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper'' (§ 201.66(c)).

(Response) We have clarified in § 207.1(a) of the final rule that the definitions and interpretations of terms in sections 201 and 510 of the FD&C Act apply to the terms used in part 207 unless otherwise defined. Accordingly, the term ''label'' means a display of written, printed, or graphic matter upon the immediate container of any article consistent with section 201(k) of the FD&C Act. The term ''labeling'' more broadly includes both immediate container labels and other written, printed, or graphic matter accompanying such article consistent with section 201(m) of the FD&C Act. When we intend to refer only to immediate container or package labels, we use the term ''label.'' More often, we use the broader term ''labeling'' in this final rule to encompass both immediate container labels and/or other written, printed, or graphic matter accompanying the drug, as the labeling definition in section 201(m) of the FD&C Act has been interpreted. The term ''content of labeling'' is defined slightly differently for human prescription drugs, human OTC drugs, and animal drugs, and the term is intended to encompass both labels and labeling.

The proposed rule (proposed § 207.1) referred only to definitions in section 510 of the FD&C Act, and the preamble to the proposed rule suggested that reference to the definitions in section 201 of the FD&C Act was intentionally omitted (71 FR 51276 at 51285). Consistent with 21 CFR 1.1(b), this final rule clarifies that the definitions in section 201 of the FD&C Act apply to the terms used in part 207.

c. Establishment. We proposed to define ''establishment'' in § 207.1 as ''a place of business under one management at one geographic location.'' The definition in proposed § 207.1 also stated ''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.''

Rather than adopt this proposed definition, the final rule retains the definition of the term ''establishment'' that has appeared in the part 207 regulations since 1980. This definition states that an establishment is ''at one general physical location.''

(Comment 7) One comment suggested that the phrase ''within the same city'' used in the proposed definition of ''establishment'' was too specific. This comment argued that a manufacturing facility located in a city with a warehouse located just outside that city should together be treated as a single establishment for registration purposes.

(Response) In reviewing this comment and considering it in light of the longstanding definition of ''establishment'' and the objectives behind the establishment registration requirement, we determined that the existing definition in part 207 is clearer and better serves our objectives than would the proposed amended definition. The longstanding language, ''one general physical location,'' generally restricts a single establishment to one street address or one or more contiguous plots of land. We do not agree with the comment that a second facility located in a different city should be covered by the first facility's establishment registration.

We note, however, that a facility operated only as a warehouse may not require registration. Section 510 of the FD&C Act and § 207.17 of this final rule

require registration of establishments where drugs are manufactured, repacked, relabeled, or salvaged. A facility at which drugs are merely stored may not require registration under this final rule, unless the facility includes, for example, controlled storage for stability testing as an element of good manufacturing practices. Other Federal and State requirements may apply to such facilities.

Likewise, the corporate headquarters of a drug establishment should not register under this rule if drugs are not manufactured, repacked, relabeled, or salvaged at that location.

d. Foreign. We proposed 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 ''establishment,'' we proposed to use ''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.

We have omitted the words ''or distributed'' from this definition because only establishments at which drugs are manufactured, repacked, relabeled, or salvaged are required to be registered.

(Comment 8) One comment urged us to revise the definition of ''foreign'' to mean ''located in a foreign country'' while stating in § 207.9 that part 207 applies to foreign entities who import or offer for import products into the United States.

(Response) We do not agree that the proposed rule was confusing or difficult to understand in this respect and have decided against making this change.

e. Importer. Section 207.25 of this final rule and section 510(i) of the FD&C Act require foreign establishments, when registering, to provide names and contact information for each importer in the United States of drugs manufactured, repacked, relabeled, or salvaged at the establishment that is known to the establishment. We proposed to define ''importer'' to mean, in part, ''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.'' In proposing this language, we recognized that a foreign establishment may have more than one importer, and we proposed 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.

(Comment 9) Some comments stated that our proposed definition of the term ''importer'' was too broad and would increase the burden on manufacturers to provide unnecessary information concerning a wide variety of entities that are not responsible for the drug. One comment noted that the inclusion of downstream recipients in our definition of ''importer'' would impose a significant reporting burden on foreign establishments that is not required of domestic establishments.

(Response) We agree that we should clarify and narrow the proposed definition of ''importer.'' As proposed, the definition included every U.S. recipient of a foreign-produced drug, excepting only the final consumer or patient. Of this large group, foreign establishments would be required to identify in their establishment registration submissions only those importers that are known to the establishment. To make this information element more useful to FDA and to reduce the burden on registered establishments, we have determined that in this context the term ''importer'' should include a U.S. owner, consignee, or recipient *at the time of the drug's entry into the United States* and should not include additional subsequent owners, consignees, or recipients of the drug. We have revised the definition of importer in § 207.1 of the final rule accordingly.

(Comment 10) One comment recommended that we change ''company or individual'' to ''person,'' in the rule's definition of ''importer,'' consistent with the definition of the term ''person'' in section 201(e) of the FD&C Act.

(Response) We agree that the term ''person,'' as defined in the FD&C Act, is an improvement over ''company or individual'' in this definition. We have made this change in §§ 207.1 and 607.3 of the final rule, and as discussed in our response to comment 6, we have also added a statement in §§ 207.1(a) and 607.3(a) that the definitions and interpretations of terms in sections 201 and 510 of the FD&C Act apply if not otherwise defined.

f. Person who imports or offers for import. Section 207.25 of this final rule and section 510(i) of the FD&C Act also require foreign establishments, when registering, to supply names and contact information for each person who imports or offers for import drugs manufactured, repacked, relabeled, or salvaged at the establishment. The proposed rule's definition of ''person who imports or offers for import'' included ''an agent, broker, or other entity, other than a carrier, that the foreign establishment uses to facilitate the import of its drug into the United States.'' We invited comments on the use and interpretation of the term ''facilitate.''

(Comment 11) Some comments expressed concern regarding the potential breadth of this definition, noting in particular that the word ''facilitate'' could, in theory, encompass entities such as foreign insurance adjusters, underwriters, and international banks. Commenters pointed out the significant burden associated with the identification of such entities in foreign establishment registrations and updates to registrations, noting that international supply chains and business relationships are not static. One comment urged FDA to exclude customs brokers from the rule's definition of ''person who imports or offers for import.'' Another comment encouraged FDA to exclude middlemen from this definition, as their identities would change frequently.

(Response) Although we did not intend for the word ''facilitate'' to be read as broadly as some comments suggested, FDA agrees that the definition of ''person who imports or offers for import'' should be made more precise, narrow, and useful.

We note, as a matter of clarification, that in section 510(i) of the FD&C Act and in § 207.25 of the final rule, the requirement that foreign establishments identify each person who imports or offers for import is not said to be limited to persons known to the establishment (unlike the requirement that they identify ''importers''). The preamble to the proposed rule included statements that were inconsistent with the FD&C Act in this regard, suggesting that foreign establishments would be required to report the name of each person *known to the establishment* who imports or offers for import its drug(s) into the United States. See, *e.g.,* 71 FR 51276 at 51289. In fact, the proposed rule (proposed § 207.25), the final rule, and the FD&C Act all require foreign establishments to report, when registering, the name of each person who imports or offers for import its drug(s) into the United States without regard to whether such persons are known to the establishment. Therefore, it is important that we define ''person who imports or offers for import'' in a way that is practical, useful, and consistent with this understanding.

Our intention in defining this term is to include foreign persons who are primarily responsible for sending a drug to the United States. Foreign establishments are reasonably expected to know the identities of such persons. In many cases, the establishment itself will be a person who imports or offers for import its drugs into the United States. In other cases, it will be a person the foreign establishment engages to send one or more drugs to the United States. It will generally be the foreign person who owns the drug and sells or enters into a contractual obligation to supply the drug to a person in the United States.

In light of the comments received and FDA's objectives, the final rule defines ''person who imports or offers for import'' to mean the owner or exporter of a drug who consigns and ships a drug from a foreign country to the United States. This definition includes persons who send a drug to the United States by international mail or other private delivery service, but does not include carriers who merely transport the drug. This definition is not intended to include persons operating merely as customs brokers.

g. Manufacture, manufacturer. The definitions of ''manufacture'' and ''manufacturer'' in § 207.1 of this final rule include minor editorial revisions for clarity and new references to animal feed bearing or containing a new animal drug.

(Comment 12) Some comments stated that the definition of ''manufacturer'' should specify that it applies only to entities manufacturing drugs for commercial distribution.

(Response) We disagree with the recommendation that the definition of ''manufacturer'' be limited to drugs manufactured ''for commercial distribution.'' The underlying statutory provisions require registration of establishments where drugs are manufactured, without regard to commercial distribution (section 510(c) of the FD&C Act), but require listing of drugs that are manufactured for commercial distribution (section 510(j) of the FD&C Act). Accordingly, under § 207.17 of this final rule, each domestic establishment where a drug is manufactured (or repacked, relabeled, or salvaged) must be registered unless exempt from registration under section 510(g) of the FD&C Act or under § 207.13, regardless of whether the drug is commercially distributed. The drug listing obligation, as described in § 207.41, applies to drugs that are manufactured, repacked, relabeled, or salvaged for commercial distribution. (See separate definition of ''commercial distribution.'')

(Comment 13) One comment asked that drug sponsors be included in the definition of manufacturer. Other comments suggested that FDA add ''product formulator'' to the definition of ''manufacturer'' or provide definitions for terms such as ''drug sponsor.'' These comments pointed out that the holder of an approved application, such as an NDA, or the formulator of a nonprescription monograph product may use a contract manufacturer to produce the product for distribution under the name of the application holder or the product formulator. Some comments recommended that the final rule treat such application holders or product formulators as manufacturers so they would register their establishments and list such products and that it exempt contract manufacturers from the drug listing requirement.

(Response) We decline to add the application holder or ''product formulator'' concepts to the definition of ''manufacturer.'' Under section 510(c) of the FD&C Act, the obligation to register drug establishments rests on owners or operators of establishments engaged in the manufacture (including repacking, relabeling, and salvaging) of drugs, and the listing obligation applies to ''every person who registers.'' FDA recognizes that this language could be read broadly to encompass entities that develop or formulate drug products without performing manufacturing operations. However, considering the objectives behind drug registration and listing, we are currently interested in the registration of establishments where manufacturing operations (including repacking, relabeling, and salvaging) take place and the listing of drugs handled at those establishments.

We recognize, however, that an application holder or a product formulator using a contract manufacturer to manufacture a drug may wish to submit drug listing information for that product directly to FDA. Although the actual manufacturer of the drug has the legal obligation to list it, FDA would accept listing information for the drug submitted by its formulator or any other person acting as an authorized agent for the manufacturer. When we use the term ''authorized agent'' in this final rule, we mean a person who is authorized to act on behalf of another. The term ''authorized agent'' should not be confused with the United States agent referred to in § 207.69(b).

(Comment 14) Several comments asked for clarification on how the terms ''manufacture,'' ''repackage,'' ''relabel'' and ''private label distributor'' would apply to the medical gas industry and pointed out that certain medical gas operations, such as the transfilling of gas from one container to another, have long been treated as drug manufacturing by FDA but, under the proposed rule, would seem to qualify as ''repacking.'' These comments asked FDA to classify medical gas refillers as ''manufacturers'' rather than ''repackers'' in the final rule.

(Response) FDA agrees that these important points require clarification. Nothing in this final rule is intended to alter the definitions applicable to FDA's regulations governing current good manufacturing practices for drug products, parts 210 and 211. Therefore, the definition of ''manufacture, processing, packing, or holding of a drug product'' currently appearing in § 210.3(b)(12) will continue to apply to medical gases as that definition has always applied.

For purposes of part 207, we will interpret the definition of ''manufacture'' in § 207.1 as including the initial manufacturing process that produces or purifies a medical gas, whether by air separation, chemical reaction, or other process. Additionally, the mixing of two or more medical gases to produce a combination would also qualify as ''manufacture'' under § 207.1. The impact of this interpretation is that a person who thus qualifies as a manufacturer of a medical gas will be required to submit the drug listing information required under § 207.49 of this final rule (''What listing information must a registrant submit for a drug it manufactures?'') in addition to registering the establishment(s) at which manufacturing is conducted.

All subsequent transfillings of a medical gas from one container to another (*i.e.,* from tanker trucks into standing tanks and from standing tanks into smaller containers, etc.) would fall within the definition of ''repack or repackage'' in § 207.1 of this final rule. The impact of this interpretation is that a person who thus qualifies as a repacker of a medical gas will be required to submit the drug listing information required under § 207.53 of this final rule (''What information must a registrant submit for a drug that it repacks or relabels?'') in addition to registering the establishment(s) at which repackaging is conducted. Comments opposing this classification expressed concern that under the proposed rule, repackers would be required to identify the NDC assigned to a drug immediately before it is received by the repacker as information that must be submitted to obtain an NDC for a repackaged drug

under proposed § 207.33(d)(1)(ii). See our response to Comment 73 regarding an exemption for medical gases from the requirement that registrants submit such source NDCs for drugs they repackage or relabel.

The definition of ''relabel'' in § 207.1 of this final rule applies to medical gases. It refers to changing or altering the existing label on a drug or drug package, without repacking the drug or drug package. A person who places a label on a repackaged drug (*e.g.,* a medical gas recently filled into a canister) for the first time qualifies as a ''repackager'' as that term is defined in this final rule.

The term ''private label distributor'' is defined in § 207.1 of this final rule to mean, with respect to a particular drug, a person who did not manufacture, repack, relabel, or salvage the drug but under whose label or trade name the drug is commercially distributed. This definition applies equally to private label distributors of medical gases and other drugs. A medical gas transfiller is a repackager, and not a private label distributor, under this final rule. As discussed in our response to comment 16, private label distributors do not—by reason of their status as private label distributors—have an obligation to register establishments or list drugs. They must have labeler codes, obtained under new § 207.33(c), and they may submit drug listing information or establishment registration information if acting as the authorized agent of a registrant on whose behalf the information is submitted.

h. Material change. In the proposed rule, ''material change'' was defined as any change in any drug listing information, excluding labeling changes in arrangement or printing or labeling changes of an editorial nature. This definition is retained in the final rule with minor revisions to clarify that material change also does not include changes in the format of labeling, or the inclusion of a bar code or the initial inclusion of an NDC on a label.

(Comment 15) One comment asked FDA to clarify the types of labeling changes that would qualify as a material change and, hence, require reporting as an update to drug listing information under § 207.57. This comment specifically suggested examples of labeling changes that would qualify as significant changes in the labeling of a prescription drug product or significant changes in the label or package insert of an OTC drug product.

(Response) In referring to ''significant'' labeling changes, this comment seems to relate to the longstanding definition of ''material change'' in § 207.3(a)(3), prior to this final rule, which encompassed labeling changes described as ''significant.'' Today's final rule revises that definition so that material change includes any labeling change other than changes in the format of labeling, changes of an editorial nature, inclusion of a bar code, or initial inclusion of an NDC. In this context, changes of an editorial nature would not include any changes that add or revise meaning.

Thus, the new definition of ''material change'' adopted as part of this final rule is broader than the previous definition and is not limited to ''significant'' changes. The definition includes—with very few exceptions—any change in previously reported drug listing information. FDA intends to rely primarily on new § 207.57 to maintain an up-to-date database of current drug labeling. Registrants should submit current labeling (and a resubmission of all listing information) each time they submit a drug listing update to report changed information under § 207.57.

i. Private label distributor. We proposed 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. In the preamble to the proposed rule we explained that the private label distributor does not engage in any activities performed by a manufacturer, repacker, relabeler, or salvager for the drug it distributes (71 FR 51276 at 51290).

In the final rule, private label distributor is defined to mean, with respect to a particular drug, a person who did not manufacture, repack, relabel, or salvage the drug but under whose label or trade name the drug is commercially distributed. We have also defined ''private label distribution'' in this final rule to mean commercial distribution of a drug under the label or trade name of a person who did not manufacture, repack, relabel, or salvage that drug.

(Comment 16) Some comments requested clarification regarding the distinction between private label distributors, manufacturers, and wholesale distributors. Others urged FDA to allow private label distributors to list the drugs they distribute. One comment requested clarification regarding the responsibilities of private label distributors under part 207.

(Response) We agree that more clarity is needed regarding these terms and the registration and listing obligations associated with private label distribution of drug products. We have eliminated the mention of establishment ownership in the proposed rule's definition of ''private label distributor'' because private label distributors do not necessarily own establishments that require registration under section 510 of the FD&C Act. We have also clarified that an entity may act as a private label distributor with respect to a particular drug. For example, if a drug manufacturer distributes, under its own name or trade name, a drug manufactured entirely by a contract manufacturer, it is acting as a private label distributor with respect to that drug. The difference between private label distributors and wholesale distributors or others involved in drug distribution is that a private label distributor's name, trade name, or label appears on the product. A common example of private label distribution is the sale of aspirin under a retail pharmacy's brand name when the retail pharmacy did not manufacture the product. As defined in this final rule, private label distribution encompasses the use of any brand name or business name on a drug product where the named business or the owner of the brand name did not manufacture the drug. Thus, as we are defining the term in part 207, a private label distributor may, but does not necessarily, operate retail stores or play a role in the physical distribution of the drug product. Even without using a brand name, if an entity is identified as the distributor or marketer of a drug under § 201.1 of the drug labeling regulations, without having manufactured the drug, that person will qualify as a private label distributor as the term is defined in this final rule.

Under this final rule, private label distributors do not have registration or listing obligations with respect to drugs for which they merely act as private label distributors. Only manufacturers, repackers, relabelers, and salvagers have an obligation to register and list. Private label distributors are subject to this final rule only in that they must apply for an NDC labeler code as described in § 207.33(c) and update the information submitted under that section when the information changes. Private label distributors are in the best position to obtain their own labeler codes and update information associated with those codes, thereby preventing potential submissions of inconsistent or inaccurate information by multiple contract manufacturers.

A person who is a private label distributor with respect to a particular drug does not for that reason incur an establishment registration or listing

obligation. The FD&C Act and the regulations in part 207 both place the registration and listing obligation on persons who manufacture, repack, relabel, or salvage drugs. The registration and listing obligation thus rests with the actual manufacturer, repacker, relabeler, or salvager whether or not a product is intended for private label distribution. For this reason, the final rule does not include provisions regarding establishment registrations or drug listings submitted by private label distributors.

We recognize, however, that some private label distributors are in a position to supply listing information, including NDCs, for drugs distributed under their names and may prefer to do so. FDA will accept registration and listing information submitted by any authorized agent acting on behalf of a manufacturer, repacker, relabeler, or salvager, and this includes a private label distributor authorized by a manufacturer, repacker, relabeler, or salvager, to submit drug listing information on its behalf. In these cases, the manufacturer, repacker, relabeler, or salvager remains responsible for compliance with all registration and listing requirements and the accuracy of the information submitted by its agent.

A person who acts merely as a wholesale distributor of a drug product (i.e, a person who did not manufacture, repack, relabel, or salvage the drug product and whose name, trade name, or label does not appear on the drug product) does not incur obligations under this rule.

j. Relabel, relabeler, repack, repacker. We proposed to define ''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 also proposed to define ''relabeler'' to mean a person who owns or operates an establishment that relabels a drug.

We proposed to define ''repack'' to mean repack or repackage or otherwise change the container or wrapper of a drug or drug package. Similarly, we proposed to define ''repacker'' to mean a person who owns or operates an establishment that repacks a drug or drug package.

In the final rule, these definitions are clarified and revised in response to comments.

(Comment 17) Some comments noted that the definition of relabel could include wholesale drug distributors who add information to outer container labels for purposes of delivery to a customer, customer identification, inventory management, special handling instructions, or to aid in compliance with Federal and State pedigree requirements. Commenters urged us not to require establishments (*e.g.,* distribution facilities) where such relabeling occurs to register and list.

(Response) We agree generally with these comments and have revised the definition of ''relabel'' in the final rule to exclude the addition or modification of information affixed solely for purposes of delivery to a customer, customer identification, or inventory management. However, we did not exclude the addition of special handling instructions from the definition of ''relabel,'' as recommended in these comments. Such an exclusion might be misinterpreted as accommodating revised storage instructions in drug labeling. However, FDA would not object to the addition of storage information to an outer label if such information is not inconsistent in any way with storage instructions appearing elsewhere in the drug's labeling. In that case, FDA would not regard the addition of such storage information to an outer container label as relabeling that would subject a person to registration and listing.

k. Representative sampling of advertisements and *Representative sampling of any other labeling.* The definitions of these terms included in the proposed rule appear in this final rule with one minor revision.

(Comment 18) The preamble to the proposed rule included a brief discussion of these definitions. That discussion pointed out a confusing aspect of the previous definitions of these terms and the previous definition of the term ''advertising and labeling'' in part 207. See 71 FR 51276 at 51291. One comment argued that there was no conflict in these definitions and urged FDA to retain our previous definitions of ''representative sampling of advertisements'' and ''representative sampling of any other labeling.'' This comment pointed out that the examples given in those previous definitions were helpful.

(Response) We disagree with this comment. The revised definitions are intended to eliminate some confusion associated with the previous definitions as explained in the preamble to the proposed rule. The examples appearing in the previous definitions read as follows: ''If more than one medical journal advertisement is used but the promotional content is essentially identical, only one need be submitted'' and ''if more than one brochure is used but the promotional content is essentially identical, only one need be submitted.'' The quoted language served as common sense guidance regarding the application of the definitions without being a central part of the definitions. Although omitting that language from the definitions included in the proposed rule and this final rule, FDA is not disavowing the examples or suggesting that registrants should take a different approach.

2. Who does this part cover? (§ 207.9)

The Agency proposed new § 207.9 to clarify the types of businesses that are subject to drug establishment registration and listing under part 207. Section 207.9 is retained in this final rule with certain revisions and clarifications.

Section 207.9(a)(3) of this final rule clarifies that private label distributors are subject to part 207. As discussed previously in this document, private label distributors do not have an obligation to register an establishment or list any drugs arising from their activities as private label distributors. They are, however, expected to obtain NDC labeler codes under § 207.33(c) of this final rule and update the information reported to FDA under § 207.33(c) as required by § 207.33(c)(2).

Section 207.9(a)(4) of this final rule is revised to state more clearly its applicability to establishments engaged in the manufacture, repacking, relabeling, or salvaging of drugs regulated under a BLA. These establishments are subject to part 207 unless they are required to register and list under part 607 (ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS).

Section 207.9(a)(5) of this final rule is revised to state that HCT/Ps, as defined in § 1271.3(d), are subject to registration and listing under part 207 if they are drugs regulated under section 505 of the FD&C Act or under section 351 of the PHS Act. A conforming amendment is made to § 1271.1. Manufacturers of HCT/Ps that are regulated under section 361 of the PHS Act (42 U.S.C. 264) and not under section 351 will remain subject to registration and listing under part 1271.

(Comment 19) Comments requested clarification on the applicability of this rule to contract manufacturers and private label distributors of drug products, saying it was not clear in the proposed rule how contract manufacturers are to handle establishment registration and labeler code assignment.

(Response) Manufacturers of drug products are obligated by the FD&C Act and by this final rule—whether or not

they are contract manufacturers—to register their establishments and list the drugs they manufacture for commercial distribution (as the term ''commercial distribution'' is defined in new § 207.1). Sections 207.49 and 207.53 of this final rule require manufacturers, repackers, and relabelers to provide their own NDC (an NDC that includes the registrant's own labeler code) for each drug they list. (Salvagers are not required to provide new NDCs when listing drugs they salvage because a drug's NDC does not change when it is merely salvaged, and not repacked or relabeled. A person who salvages and then repacks or relabels a drug is a repacker or relabeler, as those terms are defined in § 207.1, and must register and list as a repacker or relabeler.) This provision requires manufacturers, repackers, and relabelers responsible for listing drugs, including contract manufacturers, to obtain an NDC labeler code in accordance with new § 207.33(c).

When listing a human drug manufactured for private label distribution (distribution under the name or trade name of someone other than the drug's manufacturer, as defined in new § 207.1), §§ 207.49 and 207.53 require registrants to provide two NDCs, one that includes the registrant's own NDC labeler code and one that includes the NDC labeler code of the private label distributor. As stated in response to comment 16, FDA will accept drug listing information submitted by a private label distributor (or anyone else) if properly authorized to act as an agent for the actual manufacturer. The use of an agent to handle establishment registration or drug listing submissions does not, however, transfer legal responsibility for complying with this final rule from a manufacturer, repacker, relabeler, or salvager to its agent. Animal drugs manufactured for private label distribution should be listed under a single NDC that includes the labeler code of the private label distributor.

Note that the term ''private label distributor'' is defined in new § 207.1 to mean, with respect to a particular drug, a person who did not manufacture, repack, relabel, or salvage the drug but under whose label or trade name the drug is commercially distributed. FDA's statements in this document that private label distributors are not obligated to register their establishments or list the drugs they distribute are premised on this definition. If someone who would otherwise qualify as a private label distributor carries out testing or control procedures applied to the final product, *e.g.,* systematic batch release testing required under current good manufacturing practices, that person may qualify as a manufacturer (see the definition of ''manufacture'' in new § 207.1) and need to register its establishment where the testing or control procedures are carried out. (But if a private label distributor uses a contract laboratory to carry out the testing or control procedures, the contract laboratory, not the private label distributor, may qualify as a manufacturer and need to register its establishment.) Likewise, if someone qualifies as a private label distributor with respect to one or more drugs, but also qualifies as a manufacturer, repacker, or relabeler with respect to other drugs, that person would need to register the establishment where manufacturing, repacking, or relabeling is conducted and list the drugs that are manufactured, repacked, or relabeled for commercial distribution at the registered establishment.

Entities that qualify as private label distributors under this final rule and do not also manufacture, repack, relabel, or salvage any drugs may already have effective establishment registrations and drug listings submitted in the past. We do not expect these entities to renew their registrations after the effective date of this final rule. They may either cancel their registrations or allow their registrations to lapse by not making any further submissions. Any drug listings submitted in the past by entities that qualify as private label distributors under this final rule for drugs they do not manufacture, repack, relabel, or salvage should be transferred to the actual manufacturers, repackers, relabelers, or salvagers of the listed drugs.

(Comment 20) One comment asked FDA to clarify whether radiologic products are subject to this rule.

(Response) This comment did not elaborate on the types of products encompassed by the question so we are unable to respond specifically. There is not an exemption from the establishment registration and drug listing requirements for manufacturers of radioactive drugs, also known as radiopharmaceutical products. Anyone with questions about the applicability of part 207, either before or after this final rule, to radioactive drug products should contact the electronic Drug Registration and Listing System staff in the Office of Compliance at FDA's Center for Drug Evaluation and Research (CDER). For diagnostic device products that include a radioactive drug constituent part, see our response to comment 22 in this document regarding drug/device combination products. Also see part 807 regarding establishment registration and listing for radiologic device products. Positron emission tomography (PET) drugs are subject to part 207, as stated in § 207.13(l)(1) and as discussed in the proposed rule (71 FR 51276 at 51285).

(Comment 21) One comment requested guidance regarding the information needed for ''active drug substance manufacturers'' to register and list.

(Response) In this final rule, the term ''active pharmaceutical ingredient'' (API) is defined in § 207.1. The registration obligation applies to each domestic establishment that manufacturers, repacks, relabels, or salvages a drug or an animal feed bearing or containing a new animal drug (whether or not that product is commercially distributed). It also applies to each foreign establishment that manufacturers, repacks, relabels, or salvages a drug or an animal feed bearing or containing a new animal drug that is imported or offered for import into the United States. In each case, the term ''drug'' includes: (1) An API by itself, (2) an API that has been combined with one or more other APIs or inactive ingredients (see definition of ''unfinished drug'' in § 207.1), and (3) finished drug products (see definition of ''finished drug product'' in § 207.1).

The information that must be submitted for establishment registration is set forth in new § 207.25. These information elements do not differ depending on whether the registrant handles APIs, other unfinished drugs, or finished drugs.

The information that must be submitted with a drug listing is set forth in new § 207.49 for a drug the registrant manufactures, § 207.53 for a drug the registrant repacks or relabels, and in § 207.54 for a drug the registrant salvages. As specified in § 207.41, the drug listing obligation applies only to drugs that are manufactured, repacked, relabeled, or salvaged for commercial distribution. Sections 207.49, 207.53, and 207.54 indicate some minor differences in the information that must be submitted depending on whether the drug is finished or unfinished. For example, § 207.49(a)(15)(iv) describes the labeling that must be submitted for an unfinished drug.

(Comment 22) One comment asked, in the context of the proposed rule's requirement that NDCs appear on drug labels, how the rule would apply to drug/device combination products. Other comments asked how registration and listing should be handled for drug/device combination product kits. (See the definition of ''combination product'' in § 3.2(e) (21 CFR 3.2(e)), unaffected by this rulemaking.)

(Response) We acknowledge that the proposed rule did not include an explanation of its applicability to drug/device combination products, including how manufacturers of such products should register their establishments, list their combination products, and provide related information on the labels of their combination products. The codified of this final rule likewise does not contain specific provisions regarding drug/device combination products. FDA expects to further address drug/device combination product registration and listing in the future. As stated previously in this document, we also are not finalizing the proposed amendment to § 201.2 that would have required human-readable NDCs on the labels of all drugs subject to the listing requirement.

3. Who is exempt from registration and listing requirements? (§ 207.13)

The proposed rule included a new § 207.13 aimed at clarifying the types of businesses that are exempt from drug establishment registration and listing under part 207. Section 207.13 is retained in this final rule with certain revisions and clarifications. Some exemptions described in § 207.13 are derived directly from section 510(g) of the FD&C Act. Other exemptions are established under section 510(g)(5) of the FD&C Act supported by our finding that registration by such classes of persons is not necessary for the protection of the public health.

(Comment 23) Several comments argued against the elimination of two existing exemptions from registration and listing that the proposed rule would have revoked. These two exemptions encompass: (1) Drugs imported under section 801(d)(3) of the FD&C Act (often referred to as ''import for export'') and (2) drugs that enter a foreign trade zone and are re-exported from that foreign trade zone without having entered U.S. commerce.

(Response) Previous § 207.40(b) stated 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. The section also stated that this prohibition did not apply to, among other things, components of drugs imported under section 801(d)(3) of the FD&C Act. Section 801(d)(3) allows persons to import certain articles, including components of drugs, if specified conditions are met, provided that the imported articles are further processed or incorporated into products and exported or, if not used, the imported articles are destroyed or exported. Thus, previous § 207.40(b) exempted certain foreign establishments from the establishment registration and listing requirement.

Previous § 207.40(a) stated that a foreign establishment was not required to comply with the registration and listing requirements if its drug entered a foreign trade zone and was re-exported from that foreign trade zone without having entered U.S. commerce.

Upon careful consideration of the comments received, we have decided to retain both exemptions in this final rule. Therefore, under § 207.13(j) of this final rule, if all the conditions of section 801(d)(3) of the FD&C Act are satisfied, a component of a drug will not be excluded from importation into the United States by reason that it is unlisted or was manufactured at an unregistered foreign establishment. Additionally, under § 207.13(j) of this final rule, a foreign establishment does not incur a registration and listing obligation if its drug enters a foreign trade zone and is re-exported from that foreign trade zone without having entered U.S. commerce. These exemptions pertain only to drugs that are re-exported or components of drugs that are processed or incorporated into products and then exported, and these exemptions pertain only to foreign establishments. If an establishment located within a foreign trade zone manufactures, repacks, relabels, or salvages a drug for commercial distribution in the United States, that establishment would need to register and list those drugs it handles for U.S. commercial distribution. Additionally, if a foreign establishment exports drugs to the United States relying on either of these exemptions, but also exports other drugs for commercial distribution in the United States, it must comply with the registration and listing requirements for those drugs that are commercially distributed in the United States.

The corresponding exemptions for blood product establishments are also retained in § 607.40 under this final rule.

(Comment 24) One comment asked FDA to confirm that animal biological products are not subject to this rule.

(Response) Some biological drugs intended for administration to animals are regulated by the U.S. Department of Agriculture (USDA) under the Virus, Serum, and Toxins Act of 1913. Section 510.4 (21 CFR 510.4) states that animal drugs produced and distributed in full conformance with the Virus, Serum, and Toxins Act and any regulations issued thereunder shall not be deemed to be subject to section 512 of the FD&C Act (includes premarket approval and other requirements for new animal drugs regulated by FDA). As proposed in § 207.13(g), the final rule includes an exemption applicable to these products in § 207.13(h).

(Comment 25) Comments from the medical gas industry expressed concern about the ability of entities such as pharmacies, hospitals, clinics, and emergency responders to refill medical gas cylinders if the repackaging would require the repacker's NDC to appear on the label of the repackaged product. The comment stated that if these entities are exempt from part 207, they cannot obtain an NDC.

(Response) Our decision not to include the proposed amendments to § 201.2 that would have required human-readable NDCs on drug labels renders the concern expressed in this comment moot. We would like to confirm that pharmacies, hospitals, clinics, other health care entities, and public health agencies that qualify as exempt from the registration and listing requirements under § 207.13 of this final rule do not lose their exemptions by dispensing medical gases or filling medical gas containers in the normal course of their activities.

C. Registration (Part 207, Subpart B)

1. Who must register? (§ 207.17)

Section 207.17 describes who is required to register an establishment under part 207. This section is reworded in the final rule: (1) To distinguish between domestic and foreign manufacturers, repackers, relabelers, and salvagers and (2) to clarify that FDA will accept registration information submitted by a private label distributor only if it is acting as an authorized agent for and submitting information pertaining to an entity that has an establishment registration obligation.

(Comment 26) One comment asked FDA to clarify whether a storage facility that does not repack or relabel drugs is required to register under part 207.

(Response) A facility at which drugs are stored, such as a warehouse, does not need to be registered provided drugs are not manufactured, repacked, relabeled, or salvaged (as those terms are defined in § 207.1) at the facility. Note that the definition of ''manufacture'' includes sampling, testing, or control procedures applied to the final product or to any part of the process. Thus, for example, if a warehouse includes a temperature-controlled storage area where drug samples are stored for stability testing to satisfy current good manufacturing practice requirements, that activity would qualify as a manufacturing

operation and require registration of the warehouse as a drug establishment. Other State or Federal requirements may apply to such facilities.

As explained in response to Comment 17, we have revised the definitions of ''relabel'' and ''relabeler'' so they do not include the addition or modification of information affixed to drug packaging solely for purposes of delivery to a customer, customer identification, or inventory management. Therefore, the addition or modification of such information at a warehouse does not trigger the need to register it as an establishment.

2. When must initial registration information be provided? (§ 207.21)

Proposed § 207.21 described when initial registration information must be submitted for an establishment newly required to register under part 207. The provision is retained in this final rule and reorganized into paragraphs (a) and (b) for improved clarity.

(Comment 27) One comment suggested that the words ''for commercial distribution'' be added to § 207.21, suggesting that establishment registration is required only for establishments at which drugs intended for commercial distribution are manufactured, repacked, relabeled, or salvaged.

(Response) The absence of these words—''for commercial distribution''—from § 207.21 is intentional and comports with section 510 of the FD&C Act. Any establishment at which drugs are manufactured, repacked, relabeled, or salvaged must be registered under part 207, unless exempt from registration under section 510(g) of the FD&C Act or under the relevant regulations (§§ 207.13, 607.65, or 1271.15, as applicable) whether or not the drugs are commercially distributed. Accordingly, an establishment at which an investigational drug is manufactured is subject to the establishment registration requirement. The listing obligation, on the other hand, applies to drugs that are for commercial distribution.

3. What information is required for registration? (§ 207.25)

Proposed § 207.25 described the information that must be submitted to register an establishment. The provision is retained in the final rule with minor substantive and editorial revisions. Substantively, new § 207.25 no longer requires the submission of fax numbers to register establishments and now includes the new statutory requirement that registrants provide a UFI for each establishment. (See our discussion of establishment registration numbers and UFIs in section II.B, Changes to the Proposed Rule.) New § 207.25 also clarifies that the physical address of each establishment is required (rather than a post office box, for example), and a mailing address is required for the establishment's official contact.

(Comment 28) One comment asked FDA to clarify what format should be used when a foreign establishment submits contact information for each importer. This comment also asked FDA to explain who should submit establishment registration information when a business has both foreign and U.S. establishments.

(Response) According to new § 207.61, all information transmitted to FDA under part 207, including establishment registration information, must be transmitted to FDA in electronic format unless a waiver is granted. FDA's systems for electronic registration include fields for information elements such as the required contact information for U.S. importers of drugs manufactured, repacked, relabeled, or salvaged at a foreign establishment.

Section 207.17 addresses this comment's second question, who should submit establishment registration information when a business has both foreign and U.S. establishments? This section states that when operations are conducted at more than one establishment, and common ownership and control among all the establishments exists, the parent, subsidiary, or affiliate company may submit registration information for all establishments. This applies whether the establishments are domestic, foreign, or both.

(Comment 29) One comment asked FDA to exempt contract manufacturers from the requirement that establishments identify each importer in the United States of drugs they manufacture, repack, relabel, or salvage that is known to the establishment as well as each person who imports or offers for import such drugs to the United States. This comment stated that contract manufactures may not have this information.

(Response) This requirement is retained in the final rule, in § 207.25(h). The provision implements a statutory requirement (section 510(i)(1) of the FD&C Act). This requirement pertains only to foreign establishments, and it requires them to identify ''importers'' known to the establishment and ''persons who import or offer for import,'' as these terms are defined in § 207.1. Both of these definitions have been refined and narrowed in this final rule. A foreign contract manufacturer exporting drugs to the United States should be able to identify such persons.

4. What are the requirements for reviewing and updating registration information? (§ 207.29)

Section 207.29 describes the requirements for: (1) Expedited updating of certain changes to establishment registration information and (2) annual reviewing and updating of establishment registration. This section is retained in the final rule with very minor revisions. Fax numbers are no longer mentioned in § 207.29(a) because they are no longer required for establishment registration. Additionally, the dates during which the annual review and update of registration information must take place have been adjusted to match section 510(b)(2) of the FD&C Act, added by FDAAA.

(Comment 30) Some comments opposed the requirement that if no changes have occurred since the last registration, registrants certify that no changes have occurred.

(Response) The annual review and updating of establishment registration information is critical to the integrity of FDA's database. The requirement that registrants certify that no changes have occurred when that is true provides important assurance that registrants have reviewed the establishment registration information they previously submitted. Otherwise, FDA would need to interpret silence from a registrant as indicating either that the information remains up to date or that the registrant may have neglected to review and update the information. We further note that section 510(b)(1) of the FD&C Act now requires annual registration of establishments between October 1 and December 31, and the option to certify that no changes have occurred since the last registration is a minimally burdensome implementation of this statutory requirement.

Please see our response to Comment 74, which addresses this issue in the context of drug listing updates.

D. National Drug Code (Part 207, Subpart C)

1. What is the national drug code (NDC), how is it assigned, and what are its requirements? (§ 207.33)

The NDC provisions in this final rule have been revised in response to comments received on the proposed rule. Most significantly, new § 207.33:

- Allows for 11 digits in the NDC (when 10-digit combinations are exhausted).
- Reflects that registrants will propose their own NDCs for drugs they

list. Under the proposed rule, FDA would have assigned NDCs in response to submissions from registrants. Under this final rule, each registrant must propose its own NDC for each drug the registrant lists. FDA will assign the proposed NDCs to the listed drugs unless they are improperly formatted, previously assigned to a listed drug, or reserved.

- Includes new NDC formatting requirements for registrants to observe when proposing NDCs.
- Transfers some information that would have been required under proposed § 207.33(c) (What information must a manufacturer submit before we will assign an NDC number to a drug?) to information that must be included in a drug listing submission.
- Allows certain drug products to be assigned alternatively formatted NDCs if approved by the Center Director. This applies to the HCT/Ps specified in new § 207.33(b)(4) if they are minimally manipulated.
- Includes a new § 207.33(c) that explains who must obtain an NDC labeler code and how labeler codes are assigned and updated.
- Includes new provisions in § 207.33(d) that explain how a proposed NDC can be voluntarily reserved.

Comments on the NDC provisions of the proposed rule and FDA's responses are summarized in this document. This does not include some comments that have been made moot by the revisions summarized previously.

(Comment 31) FDA received many comments opposing the proposed rule's requirement that FDA, rather than registrants, generate and assign the complete NDC for drugs that are subject to listing. Some comments were concerned about possible delays associated with NDC request submissions. Others were concerned about losing control over numbering conventions that individual registrants may apply to their own product codes and package codes. One comment expressed concern that subjecting OTC monograph products to an NDC assignment process could begin to resemble an FDA approval process for such products.

(Response) The objective behind FDA's proposal to generate and assign NDCs was to assure they are assigned appropriately. Although we did not intend FDA's issuance of NDCs to be time consuming or to operate as an approval process, we recognize that FDA's objectives can be met in a way that is more flexible and less burdensome for registrants. Accordingly, the proposed requirement that FDA generate the complete NDC for each listed drug is not included in this final rule.

Under new § 207.33(d), registrants, not FDA, will generate NDCs for assignment to their listed drugs. An NDC is considered to be ''proposed for assignment'' when a registrant submits it for the first time with drug listing information in accordance with § 207.49 or § 207.53. If the proposed NDC conforms to the formatting requirements of § 207.33, is not reserved for a different drug, and was not previously assigned to a different listed drug, FDA will assign the proposed NDC when it receives all required listing information for the drug.

(Comment 32) Some comments asked how far in advance of marketing a drug for the first time an NDC may be requested. Comments also pointed out that manufacturers need to know the NDC for a drug in development prior to the time of drug listing.

(Response) As explained in response to Comment 31, this final rule requires registrants to propose their own NDCs for drugs they list. FDA will assign a proposed NDC to the drug identified by the registrant if the proposed NDC conforms to the formatting requirements of § 207.33, is not reserved for a different drug, and was not previously assigned to a different listed drug.

We recognize that a mechanism for reserving a specific NDC may be helpful, as this would provide greater certainty that a proposed NDC will be accepted by FDA when it is included with a listing submission at the time of marketing. Accordingly, this final rule includes a new § 207.33(d)(3) that allows a person to voluntarily reserve a proposed NDC for a period of 2 years prior to its inclusion in a drug listing submission for the first time. Note that an NDC reserved under § 207.33(d)(3) would need to include most importantly a labeler code and a product code. At the discretion of the person submitting the reservation request, a single package code could be included, or not, with one or more package codes included later in NDC(s) submitted with complete drug listing information.

Certain minimal information must be submitted to reserve a proposed NDC, as specified in new § 207.33(d)(3). This information does not include identification of the drug's inactive ingredients. Many comments opposed the inclusion of such detailed information in the proposed rule's provision governing NDC requests.

NDCs reserved under § 207.33(d)(3) would be reserved for 2 years unless the person whose labeler code is included in the NDC asks FDA to cancel the reservation earlier. If a reserved NDC is not used during the 2-year reservation period (*i.e.,* is not submitted to FDA with complete listing information for the drug matching the reservation), the NDC will be available for assignment to another drug. Anyone wishing to extend an NDC reservation beyond 2 years may submit another reservation request.

In addition to the procedure established under § 207.33(d)(3), a registrant wishing to reserve an NDC also has the option of submitting complete listing information for a drug that is under development and specifying a future ''start marketing date'' in the listing submission. That listing submission could then be updated, as needed, when the actual marketing date arrives.

(Comment 33) One comment questioned how, when listing a drug for the first time, a registrant can supply a drug's labeling if the labeling must include the drug's NDC, and if the NDC is not assigned until the drug is listed.

(Response) As explained in response to Comment 1, unlike the proposed rule, this final rule does not require NDCs to appear in human-readable form on drug labels (but an intervening statutory amendment, the DSCSA, does require NDCs to appear as part of the product identifier on certain drug labels). After the effective date of this final rule, our regulations will continue to encourage, but not require, the appearance of human-readable NDCs on drug labels (§ 201.2) and continue to require that NDCs appear in bar codes on drug labels (§ 201.25(c)).

Under this final rule, unlike the proposed rule, registrants are able to develop and propose their own NDCs to FDA. Upon receipt of a first-time listing submission, FDA will assign the NDC proposed by the registrant to the drug being listed unless the NDC is improperly formatted, reserved for a different drug, or was previously assigned to a different listed drug. Registrants are also able to reserve an NDC for a drug under development under § 207.33(d)(3) of this final rule. Accordingly, registrants should not have difficulty determining, with adequate certainty, the NDC for a drug under development.

(Comment 34) Some comments supported the proposed rule's revocation of then-current § 207.35(b)(4)(ii), which stated that the product code of a discontinued product could be reassigned to another product 5 years after the expiration date of the discontinued product or, if there is no expiration date, 5 years after the last shipment of the discontinued product. Commenters generally agreed that the reuse of old NDCs for a different

product in the future can be confusing. One comment, however, urged FDA to allow for the reuse of NDCs.

(Response) FDA is retaining this general prohibition against the reuse of NDCs in the final rule. As indicated in new § 207.33(d)(2), an NDC will not be assigned to a drug if it was previously assigned to a different drug. The prohibition against reuse of NDCs applies to listings submitted on or after the effective date of this final rule. Drugs that are currently listed under NDCs that have been reused in accordance with previous § 207.35(b)(4)(ii) may continue to be listed under such NDCs.

Conversely, if a registrant reintroduces a drug it listed and discontinued in the past, that registrant must list the drug using the same NDC under which it was listed in the past. See § 207.37(b) of this final rule. However, if the reintroduced drug includes changes, compared to the discontinued drug, that would warrant a new NDC under new § 207.35, then it should be listed under a new NDC.

As discussed in response to Comment 19, under new § 207.49, if a private label distributor uses a contract manufacturer to produce a human drug, the contract manufacturer has an obligation to list the drug under two NDCs, one that includes the labeler code of the contract manufacturer and one that includes the labeler code of the private label distributor. If the private label distributor switches to a new contract manufacturer in the future, that new contract manufacturer would also have an obligation to list the drug under two NDCs, one that includes its own labeler code and one that includes the labeler code of the private label distributor. The NDC that includes the new contract manufacturer's labeler code will obviously differ from the NDC under which the previous contract manufacturer listed the drug (because the labeler codes will differ). The NDC that includes the private label distributor's labeler code may be the same as that under which the previous contract manufacturer listed the drug provided: (1) There have been no changes to the drug that warrant a new NDC under § 207.35 and (2) the previous contract manufacturer updates its listing information to indicate it no longer manufactures the drug (as it is required to do under § 207.57 at the time of its next June or December listing update, or sooner at its discretion). If those two conditions do not exist, FDA would accept a listing from the new contract manufacturer under a new NDC that includes the private label distributor's labeler code.

(Comment 35) We received several comments concerning the format of the NDC. Many comments expressed concern about the impact of any changes in the NDC format on various systems that track and use NDCs. Some comments urged FDA to retain the 10-digit NDC format. Others encouraged the adoption of a standard 11-digit NDC. Some comments opposed the possible introduction of alphanumeric NDCs, preferring all numeric NDCs. Others were concerned about the possible coexistence of 10- and 11-digit NDCs.

(Response) FDA is sensitive to these concerns. Section 207.33(b) of this final rule specifies the format of an NDC recognized by FDA. The final rule necessarily includes more specifications than did the proposed rule concerning NDC formatting because under the final rule, registrants, not FDA, develop their own proposed NDCs, and they must all meet certain formatting parameters. The final rule states, for example, that the NDC is 10 or 11 digits to preclude the submission of longer NDCs.

Our regulations have long stated that FDA will expand the labeler code from five to six numeric characters when the available five-character code combinations are exhausted (previous § 207.35(b)(2)(i)). This occurrence is mathematically inevitable and is reflected in new § 207.33(b)(1), which states that the NDC must consist of 10 or 11 digits. FDA will begin issuing 6-digit labeler codes, leading to 11-digit NDCs, only when the available 5-digit labeler codes are exhausted. FDA will not assign 11-digit NDCs until we begin to issue 6-digit labeler codes.

FDA recognizes the desirability of a single, standard format for NDCs, having three segments of consistent lengths, as we eventually transition to six-digit labeler codes. We intend to initiate a public discussion of future formatting options in the near future. In the meantime, the provisions included in this final rule are intended to accommodate the range of existing NDC formats, leaving room for necessary expansion to 11 digits.

This final rule refers to the NDC as a numeric code, not an alphanumeric code. This takes into account comments that objected to the inclusion of alpha characters in NDCs as disruptive of current systems and practices.

(Comment 36) Some comments urged FDA not to require NDCs for HCT/Ps, citing the International Society of Blood Transfusion (ISBT) number as a better means of identifying these products.

(Response) In response to these comments, § 207.33(b)(4) of this final rule states that an alternatively formatted NDC may be used for certain identified HCT/Ps if they are minimally manipulated and if the alternatively formatted NDC is approved by the Center Director (CDER or CBER, as appropriate). Such approval may be indicated in Guidance for Industry issued by one or both Centers or in this preamble, for example. Accordingly, FDA identifies ISBT–128 as a currently approved alternatively formatted NDC to identify HCT/Ps within the scope of § 207.33(b)(4). ISBT–128 is an international standard for the identification of medical products of human origin. Please note that an alternatively formatted NDC approved under § 207.33(b)(4) qualifies as an NDC. HCT/Ps that are not within the scope of § 207.33(b)(4) require traditionally formatted NDCs.

(Comment 37) One comment encouraged FDA to allow a single NDC, with a single package code, to be assigned to an API, which may be commercially distributed in various quantities.

(Response) This comment refers to APIs, but the question applies to any bulk product supplied in variable quantities. We would like to accept non-numeric characters, such as one or more asterisks, in the package code segment of an NDC to indicate a bulk product supplied in various quantities (as was previously done in paper submissions). However, the SPL format, currently specified in the electronic registration and listing guidance, does not accommodate non-numeric characters. Manufacturers in this situation may adopt a variety of practices. They may submit multiple NDCs with package codes corresponding to a variety of commonly ordered package sizes. They may submit an NDC package code corresponding to 1 kilogram (kg), for example, and then treat a shipment of 10 kg as being comprised of 10 units. In some cases, they may submit an NDC with a package code corresponding to a 55-gallon drum, for example, and use that packaging to ship 55-gallon orders as well as orders that are slightly less than 55 gallons in volume.

(Comment 38) One comment recommended that the NDC for a drug that was repacked or relabeled include the product code of the source drug.

(Response) Section 207.53 of this final rule requires repackers and relabelers to list drugs they repack or relabel and requires them to submit an appropriate NDC for each such drug that includes the repacker's/relabeler's labeler code. It would not be feasible to require the NDC for a repacked or relabled drug to include the labeler code of the repacker or relabeler combined with the product code of the source drug. Such a

requirement might produce an NDC that was previously assigned to a different drug. Because registrants will continue to propose their own NDCs under this final rule, a repacker or relabeler may generally adopt the convention proposed in the comment, but may not list a drug under an NDC that was previously assigned to a different listed drug.

Listing submissions for repacked or relabeled drugs must also include the complete NDC assigned to each finished drug received by the registrant for repacking or relabeling (*i.e.,* the source drug), so this link will exist in the drug's listing information.

(Comment 39) Two comments asked whether FDA will assign NDCs to products that do not have application numbers, *i.e.,* products that are not the subject of an approved application.

(Response) This question was posed in the context of the proposed requirement that registrants request an NDC from FDA by submitting information specified in proposed § 207.33(c) prior to a listing submission. In the case of finished drugs, proposed § 207.33(c) would have allowed registrants to submit an approved U.S. application number in place of certain information. As discussed in response to Comment 31, this final rule allows registrants to propose their own NDCs with listing submissions, and FDA will accept those proposed NDCs unless they are formatted incorrectly, reserved for a different drug, or previously assigned to a different drug. Under this final rule, NDCs are still ''assigned'' only by FDA, after all required listing information is received. We affirm that NDCs will be assigned in this manner to all drugs subject to the listing requirement, including drugs that do not have application numbers. As we have stated in the past (*e.g.,* previous § 207.39 and in the preamble to the proposed rule (71 FR 51276 at 51305)), FDA's assignment of an NDC does not in any way denote FDA approval of a product. Section 207.37 of this final rule states that a product may be deemed misbranded if an NDC is used to denote or imply FDA approval.

(Comment 40) Some comments asked how NDCs will be assigned to multidrug kits. Here we are addressing kits that do not contain medical devices. (See related discussion of drug/device combination products in response to Comment 22.)

(Response) If a product contains more than one finished drug product, co-packaged as a kit, and that kit is commercially distributed, the kit itself must be listed in accordance with § 207.41, under § 207.49 or § 207.53, as appropriate. A registrant submitting the listing should propose an NDC for the kit itself, distinct from any NDCs assigned to individual drug constituents contained in the kit. The NDC proposed for the kit should include the labeler code of the registrant obligated to submit the listing. If the kit is packaged for private label distribution, it should be listed under an additional NDC that includes the labeler code of the private label distributor.

(Comment 41) A comment asked whether a finished drug product, manufactured under one approved application at two different manufacturing sites under the same ownership and control could be listed under a single NDC. In this example, the finished product from each manufacturing site would have the same composition and physical appearance. The comment also asked whether the answer would change if the manufacturing sites are located in two different countries.

(Response) Each manufacturing site would need its own establishment registration under § 207.17 unless exempt under section 510(g) of the FD&C Act or under § 207.13. (Foreign establishments must register only if they manufacture, repack, relabel, or salvage drugs that are imported or offered for import into the United States.) With respect to the drug listing requirement, the proposed rule and the final rule specify in § 207.41(a) that when operations are conducted at more than one establishment, and common ownership and control exists among all the establishments, the parent, subsidiary, or affiliate company may submit listing information for any drug manufactured, repacked, relabeled, or salvaged at any such establishment. This language allows a registrant that manufactures a drug at more than one of its own establishments to submit a single listing for that product, while identifying all establishments where the registrant manufactures the drug under § 207.49(a)(12). The listed drug would have a single NDC in this scenario. The answer does not change if one or more manufacturing sites are located outside the United States.

Note, however, that FDA would also accept multiple listings if a manufacturer in this situation wished for any reason to submit separate listings and NDCs for the same drug manufactured at multiple establishments.

This analysis does not apply to an entity that uses one or more contract manufacturers to manufacture, repack, relabel, or salvage a drug. In that case, each contract manufacturing site must be registered under § 207.17, unless exempt under section 510(g) of the FD&C Act or under § 207.13. If more than one contract manufacturing site is used, and those sites are under common ownership and control, the contract manufacturer could submit a single listing for this drug covering its activities at multiple sites (also listing other drugs it is required to list under § 207.49 or § 207.53). Furthermore, as discussed in our response to comment 19, contract manufacturers must generally list a drug under two NDCs, one that includes the contract manufacturer's labeler code and one that includes the private label distributor's labeler code. In this scenario, a single NDC that includes the private label distributor's labeler code could be used with a drug manufactured at multiple contractor sites along with a single NDC that includes the contract manufacturer's labeler code, provided there are no differences in the product produced at the various sites that would warrant a new NDC under § 207.35.

(Comment 42) One comment asked how registrants should assess whether their existing NDCs comply with this rule. Some comments noted a statement in the preamble to the proposed rule that FDA intends to validate that current NDCs comply with the new regulations when the rule is finalized (71 FR 51276 at 51280) and requested more information about this process.

(Response) This final rule is not intended to require extensive changes to NDCs themselves. The NDC formatting provisions of new § 207.33(b) are intended to accommodate NDC formats currently in use. The 10-digit NDC formats provided for under § 207.33(b) of this final rule include (in terms of numbers of digits in the labeler code, product code, and package code respectively) 4–4–2, 5–3–2, and 5–4–1. Any NDC in one of those formats that is not assigned to multiple drug products and is not assigned to a non-drug product should comply with this final rule. When five-digit labeler codes are exhausted, FDA will begin issuing six-digit labeler codes, allowing for additional formats of 6–3–2 and 6–4–1.

(Comment 43) Some comments encouraged FDA to permit one registrant or business to maintain more than one labeler code. These comments pointed out that mergers and acquisitions in the pharmaceutical industry result in corporate entities responsible for drugs listed under multiple NDC labeler codes. Consolidation of such NDCs to a single labeler code would be burdensome and may not be possible in some cases if, for

example, one product code has been used with two different labeler codes.

(Response) FDA agrees with this comment. We encourage registrants and private label distributors to maintain a single labeler code wherever possible. But FDA will not require each registrant and private label distributor to maintain only one labeler code. This flexible approach accommodates mergers and acquisitions. It departs from a statement in the preamble to the proposed rule that only one labeler code would be used for new NDC numbers that FDA would have assigned prospectively for any given manufacturer, repacker, or relabeler (71 FR 51276 at 51299). It also accommodates situations in which any registrant wishes to maintain different labeler codes for different product lines or situations in which a registrant risks exhausting all available labeler code and product code combinations if the registrant operates with a single labeler code. Importantly, new § 207.33(c)(2) requires each person who is assigned a labeler code to update the information required under § 207.33(c)(1). This will allow FDA to reliably associate every labeler code with the person to whom it is assigned and the person's contact information.

Registrants and private label distributors who currently have NDC labeler codes but for whom FDA does not have up-to-date information described in § 207.33(c)(2) on the effective date of this rule are required to update their information. FDA may refuse to accept new drug listings that include an NDC labeler code for which the information required by § 207.33(c)(2) is not current in our system.

(Comment 44) One comment asked FDA to confirm that a business owning many registered establishments may maintain only one labeler code, so that all of its NDCs include a single labeler code.

(Response) FDA prefers that such a business maintain only one labeler code, and that it use this single labeler code when proposing NDCs for drugs it manufactures, repacks, relabels, or salvages at establishments under common ownership and control. However, as explained in our response to Comment 43, FDA will not require any business to maintain only one labeler code.

(Comment 45) One comment interpreted the proposed rule as preventing an entity that does not distribute its own products from maintaining its own labeler code. The comment recommended that such an entity not be required to assume distribution responsibilities to retain its labeler code.

(Response) FDA is not certain whether this comment is concerned with which NDC would have been required to appear on product labels had we finalized the proposed amendments to § 201.2, or more generally concerned with the NDCs under which private label distributor products are listed. Under § 207.33(c) of this final rule, a labeler code must be requested and maintained by any person who engages in manufacturing, repacking, relabeling, or private label distribution of drug products. The term ''private label distribution'' is defined in § 207.1 of this final rule to mean commercial distribution of a drug under the label or trade name of a person who did not manufacture, repack, relabel, or salvage that drug. A private label distributor does not need to physically engage in drug distribution to qualify as a private label distributor under this definition and maintain a labeler code under § 207.33(c).

(Comment 46) One comment gave an example of two establishments ''located in the same geographical location within two cities located five miles apart'' and asked whether those establishments would need separate NDC labeler codes and registration numbers.

(Response) Under the final rule's definition of ''establishment,'' two establishments located 5 miles apart would not qualify as being at ''one general physical location'' and would therefore require two separate registrations. Each establishment would be associated with its own UFI and establishment registration number. As stated in § 207.17 of this final rule, when operations are conducted at more than one establishment and common ownership and control among all the establishments exists, the parent, subsidiary, or affiliate company may submit registration information for all establishments. Likewise, with respect to drug listing information, § 207.41 states that when operations are conducted at more than one establishment, and common ownership and control exists among all the establishments, the parent, subsidiary, or affiliate company may submit listing information for any drug manufactured, repacked, relabeled, or salvaged at any such establishment. A single labeler code may be used in the NDCs for all drugs proposed by such a parent, subsidiary, or affiliate company.

(Comment 47) A comment asked FDA to confirm that the NDC assignment requirement for APIs applies to all APIs, whether they are supplied by domestic or foreign establishments.

(Response) Any drug, including an API, manufactured at a domestic establishment for commercial distribution in the United States must be listed under § 207.49 unless exempt under § 207.13. As proposed and under this final rule, the registration and listing requirements apply to foreign establishments whose drugs, including APIs, are imported or offered for import into the United States. See §§ 207.13(j), 207.49, and 207.53.

(Comment 48) Some comments urged FDA to exempt allergenic extract products from the NDC requirement or from drug establishment registration and listing generally. These comments argued that the proposed rule would require manufacturers of allergenic extracts to manage a large number of NDCs without obvious benefits.

(Response) Allergenic extracts are used in the diagnosis and treatment of allergies. As such, they are appropriately regulated as drugs under the FD&C Act and FDA's regulations. Section 510 of the FD&C Act authorizes FDA to exempt certain persons from establishment registration (and hence listing) if registration ''is not necessary for the protection of the public health.'' We decline to make this finding for allergenic extracts. Such an exemption would diminish FDA's ability to inspect establishments at which allergenic extracts are manufactured and track marketed products.

Both before and after this final rule, our regulations in part 207 have required that each listed drug product have an NDC. We understand that this requires manufacturers of allergenic extracts to associate a unique NDC with each product they manufacture for commercial distribution, and this may result in a large number of NDCs. We believe the public health benefits associated with drug registration and listing outweigh the burden this places on manufacturers to manage a large number of NDCs.

(Comment 49) One comment asked whether drug samples are subject to the NDC requirement.

(Response) Under this final rule, registrants must list drugs they manufacture, repack, relabel, or salvage for commercial distribution. The term ''commercial distribution'' is defined in a way that encompasses free samples. Because any listed drug requires an NDC, drugs packaged for distribution as promotional samples are expected to have NDCs.

(Comment 50) Some comments recommended that pharmacy compounded drugs be eligible for NDC

assignment. These comments noted that hospital pharmacies use the NDC to reduce medication errors.

(Response) Drug products compounded by a licensed pharmacist or a licensed physician in conformance with section 503A of the FD&C Act are generally exempt from drug establishment registration and listing under part 207 before and after this final rule, consistent with the exemptions for pharmacies and practitioners in section 510(g) of the FD&C Act. The DQSA added section 503B to the FD&C Act. Under section 503B, a compounder can register with FDA as an ''outsourcing facility.'' Because the FD&C Act now establishes a separate registration and drug product reporting process for such outsourcing facilities, this final rule exempts outsourcing facilities from the registration and listing requirements of part 207. (See new § 207.13(k).)

Compounders that meet the conditions for exemption from registration and listing requirements under part 207 may elect to voluntarily register and list their products under part 207 and obtain NDCs.

2. What changes require a new NDC? (§ 207.35)

Section 207.33(f) of the proposed rule identified the types of changes to a drug that require a new NDC. This final rule includes new § 207.35 that states with greater clarity the types of changes to a drug that require a new NDC. Substantively, new § 207.35 is similar to the corresponding requirements in the proposed rule, but the provision does not require a new NDC when changes are made to inactive ingredients or when the Drug Master File number or Veterinary Master File number, if any, assigned to an API changes.

(Comment 51) Some comments were concerned about the types of changes to a drug that would require a new NDC in the proposed rule. In particular, many comments opposed the proposed requirement that changes in a drug's inactive ingredients would necessitate a new NDC.

(Response) This proposed requirement—that a change in a drug's inactive ingredients would necessitate a new NDC—has not been retained in the final rule. Under both the proposed rule and the final rule, any change in information submitted with a drug listing must be reflected in an updated listing under § 207.57. Certain more significant changes also require a new NDC, as specified in new § 207.35. Upon careful consideration, we agree with those comments that stated it would be unreasonably burdensome to require registrants to submit a new NDC each time they change the inactive ingredient composition of a product.

Some comments questioned the scope of the proposed requirement: Would it apply to changes from one inactive ingredient supplier to another? Would it apply to changes in the quantity at which an inactive ingredient is used? Would it apply to changes in the compositional specifications of an inactive ingredient?

The justification for this requirement suggested in the proposed rule was that some patients may be sensitive to certain inactive ingredients, and a change in NDC would flag for those patients and their pharmacists and health care providers that a drug's composition may have changed (or that some other characteristic identified in § 207.35 changed).

Upon careful consideration, we agree with those comments that challenged this justification. Paying attention to changes in NDCs would be an inexact way for patients, pharmacists, and health care providers to discover changes in inactive ingredients. As proposed and under this final rule, updates to drug listing information (including a new NDC) will be submitted each June and December, or sooner at the registrant's discretion. Thus, manufacturers will not be obligated to change an NDC immediately upon changing an inactive ingredient and update the NDC on their labels on a batch specific basis.

Comments pointed out that, particularly in the case of OTC monograph products, manufacturers currently have the flexibility to use certain inactive ingredients interchangeably. FDA's current guidance regarding the labeling of OTC drug products acknowledges this practice and includes formatting recommendations to accommodate the practice.[2] The proposed rule did not explain, for example, how the new NDC requirement would apply in a situation where the manufacturer of an OTC monograph product may have switched inactive ingredients in several different batches in the 6 months leading up to a semiannual listing update submission.

Rather than impose this burden on some manufacturers, and recognizing that ingredient labeling and reference to batch numbers are more useful and exact ways to ascertain a drug's composition, this final rule does not require a new NDC when a drug's inactive ingredients change.

[2] See the guidance for industry ''Labeling OTC Human Drug Products—Questions and Answers,'' December 2008, pp. 10–11, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs).

(Comment 52) One group of comments expressed concern about the many situations in which a new NDC would be needed under the proposed rule. In addition to mentioning changes in inactive ingredients, the comments cited any addition to a drug's label or labeling, including the addition of stickers with delivery and handling instructions and ''any material change to a drug's labeling or packaging insert'' as things that should not warrant a new NDC. The comments emphasized the burden associated with changes to a drug's NDC.

(Response) Several changes in this final rule will reduce the number of occasions when a drug requires a new or additional NDC, compared to the proposed rule. See the response to comment 51 regarding changes to inactive ingredients. See our response to Comment 17 regarding the revised definition of ''relabel'' in the final rule to exclude the addition or modification of information affixed solely for purposes of delivery to a customer, customer identification, or inventory management. Under this final rule, changes or additions to a label that do not qualify as relabeling do not necessitate a drug listing submission and NDC under § 207.53. Section 207.35 of this final rule does not include ''any material change'' to a drug's labeling or package insert among the changes that necessitate a new NDC. Labeling changes are generally not included in new § 207.35. Some labeling changes will be incidental to the changes included in new § 207.35 (*e.g.,* a change to a drug's established or proprietary name), but labeling changes themselves do not trigger the need for a new NDC under this final rule. FDA has also determined that changes in Drug Master File numbers or Veterinary Master File numbers describing APIs, alone, should not necessitate new NDCs. Changes in APIs themselves, *i.e.,* a change in the identity of an API, will continue to necessitate new NDCs under new § 207.35.

(Comment 53) The Animal Health Institute noted that Animal Drug User Fee Act (ADUFA) fees are assessed for each animal drug NDC. This comment pointed out that manufacturers of animal drug products will be potentially charged twice for a single drug product due to a change in the NDC during a fiscal year or due to multiple listings for a single product required under this final rule. The comment urged FDA to exempt animal drug manufacturers from paying such extra product fees imposed by this final rule.

(Response) As noted in our response to Comment 52, several changes in this

final rule will reduce the number of occasions when a drug requires a new or additional NDC, compared to the proposed rule. Under ADUFA, the term ''animal drug product'' means each specific strength or potency of a particular active ingredient or ingredients in final dosage form marketed by a particular manufacturer or distributor, which is uniquely identified by the labeler code and product code portions of the NDC, and for which an animal drug application or a supplemental animal drug application has been approved. See section 739(3) of the FD&C Act. Because product fees are assessed under ADUFA for animal drug products meeting this definition, fees are not assessed for unfinished animal drugs or animal drugs that are not marketed. However, there may be instances where a change is made to a marketed animal drug product that necessitates a new NDC for that product during a single fiscal year, resulting in a new ADUFA product fee. This is an issue that has existed prior to this final rule.

(Comment 54) One comment asked whether a new NDC will be required when a manufacturer changes to a new supplier of an API or, relatedly, whether multiple NDCs would be needed if multiple suppliers of an API are indicated in an approval application for a finished drug product.

(Response) Section 207.35 of this final rule requires a new NDC when there is a change to any API. This provision includes changes from one API to another (*e.g.,* a change from acetaminophen to ibuprofen) and changes in the strength of an API. The provision does not encompass changes in suppliers and does not require multiple NDC product codes corresponding to multiple API suppliers.

(Comment 55) One comment requested clarification regarding when a change in drug product strength will require a new NDC (or when multiple strengths will require multiple NDCs). This comment distinguished between concentration and strength.

(Response) Section 207.35 of this final rule requires a new NDC if the strength of any API changes. The term ''strength'' is generally used to refer to the absolute quantity of API in a single unit dose (*e.g.,* 250 milligrams (mg) per tablet). Concentration, on the other hand, refers to the amount of an ingredient per defined weight or volume of product (*e.g.,* 1 mg/1 milliliter (mL)). Examples of multiple strengths requiring separate NDCs include 100 mg/tablet, 250 mg/tablet, 1 mg/1 mL, and 2 mg/2 mL. Each of these would require its own NDC if each is supplied as a unit dose. This is true even though the last two concentrations are equivalent.

(Comment 56) Some comments questioned whether two digits are sufficient for the package code segment of the NDC. Relatedly, some comments requested clarification regarding the need for a new NDC when changes are made to a drug's package size or type. For example, would a change from one type of plastic bottle to another necessitate a new NDC? Another comment argued that changes in medical gas packaging should not necessitate many new NDCs.

(Response) A 2-digit package code segment accommodates 100 different packaging configurations, counting ''00'' as one possibility.

There should be a separate package code for each package size. Therefore, if a package is enlarged to hold more of a drug product, it would need a new NDC.

A change in package configuration, such as a change from a bottle to a blister pack, would also require a new NDC.

Under new § 207.35(c), a new NDC (specifically a new package code segment) is needed for changes in the composition of packaging material that are significant enough so that the packaging type description previously submitted is no longer accurate. When submitting drug listing information electronically, registrants are currently prompted to identify the package type by selecting a choice from a drop down list. For example, ''Bottle, Plastic'' is currently one available selection in the drop down list. If a registrant originally described its packaging material using this term and later switched from one type of plastic bottle to another, there would be no need for a new NDC. But if a change in packaging material is more significant, from plastic bottle to glass bottle, for example, so that a new package type should be selected from the drop down list, FDA would require a new NDC with a new package code segment to accompany the revised listing under § 207.35(c). (This discussion pertains only to drug listing obligations. Please see the FDA guidance for industry on ''Container Closure Systems for Packaging Human Drugs and Biologics'' (May 1999, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) regarding filing requirements for changes to container closure systems in the case of drug products that are the subject of an approved application (NDA, abbreviated new drug application (ANDA), or BLA)).

Medical gases are generally packaged in tanks, canisters, or cylinders. A registrant listing a medical gas would choose the appropriate packaging type from the drop down list, populated with such terms, in our electronic drug establishment registration and listing system. We do not currently require more detail about the composition of a tank, canister, or cylinder in which a medical gas is packaged and would not require a listing update or a new NDC if the composition of a tank, canister, or cylinder changes. Therefore, we do not anticipate an unreasonable proliferation of NDCs associated with medical gas packaging under this final rule.

If a registrant exhausts all 100 package codes for a single product, that registrant may add a second product code, effectively making 100 more package codes available. This provision is reflected in § 207.35(c) of this final rule.

(Comment 57) One comment stated that many minor changes are made to a drug's packaging, such as resin composition and size optimization. This comment stated that these minor changes are already the subject of submissions to FDA, for example, as an annual report (submitted under § 314.81(b)(2)), a prior approval supplement to an NDA, or a changes-being-effected supplement. This comment implicitly questioned the need for new NDC package codes triggered by these changes.

(Response) Section 207.35(c) of this final rule requires new NDCs, specifically new package codes, when changes are made to a drug's package size or type. See our response to comment 56 regarding our interpretation of this requirement. We acknowledge that certain postapproval packaging changes are reported to an NDA, BLA, or ANDA consistent with current § 314.70 and FDA *http://www.fda.gov/Drugs*s guidance for industry ''Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry Manufacturing, and Controls Documentation'' (May 1999, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) and to a new animal drug application (NADA) or an abbreviated new animal drug application (ANADA) consistent with current § 514.8 and FDA's guidance for industry ''Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANDA'' (May 2007, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)). These submissions, however, do not duplicate or satisfy the Agency's objectives behind drug listing and the use of the NDC to identify individual marketed drug products. These submissions also are

not made for drugs that are not subject to the new drug approval requirements.

3. What restrictions pertain to the use of the NDC? (§ 207.37)

Proposed § 207.37 set forth restrictions pertaining to the use of NDCs. These provisions are retained in the final rule with minor revisions. New § 207.37 clarifies that a product improperly bearing an NDC may be deemed to be misbranded. Additionally, new § 207.37 is not addressed only to ''manufacturers, repackers, and relabelers.'' Persons who are not subject to part 207 are cautioned against concluding that the restrictions stated in § 207.37 do not apply to them. Improper use of an NDC, as described in § 207.37, may result in a misbranding charge under the FD&C Act, whether or not the responsible party is generally subject to part 207.

(Comment 58) One comment agreed that NDCs should not appear in the labeling of dietary supplements, foods, and medical devices, but encouraged FDA to exercise enforcement discretion in this area. Other comments urged FDA to permit the use of NDCs on medical devices and medical foods. Others asked FDA to implement an alternative identification system for medical devices before finalizing this rule.

(Response) Section 207.37 of this final rule states that a product may be deemed to be misbranded if an NDC is used on the product but it is not subject to part 207. Since publication of the proposed rule, FDA has issued a final rule requiring UDIs on medical devices (78 FR 58786, September 24, 2013). Section 801.57 of that rule (21 CFR 801.57) generally prohibits the use of an NDC on the label of a medical device after the date on which it must bear a UDI.

The use of an NDC on the label of a product that is not regulated as a drug may confuse and mislead consumers and health care providers into believing FDA regulates the product as a drug. Any enforcement actions in this area will be subject to a determination that a product violates § 801.57 or is misbranded, or otherwise violates the FD&C Act.

(Comment 59) One comment argued against the proposed rule's prohibition against the use of NDCs on non-drug products and asked, if this prohibition is retained in the final rule, how long manufacturers of such products would have to remove NDCs from their labels.

(Response) Please see our response to comment 58 regarding the nature of § 207.37, specifically our clarification that the use of NDCs in the labeling of non-drug products may be handled as misbranding violations or as violations of § 801.57 as appropriate. See FDA's Unique Device Identifier rule (78 FR 58786) and any guidance FDA may issue regarding the compliance deadline for § 801.57. When an NDC in the labeling of a non-drug product creates the misleading impression that FDA regulates the product as a drug, that product may be subject to enforcement action.

E. Listing (Part 207, Subpart D)

1. Who must list drugs and what drugs must they list? (§ 207.41)

Proposed § 207.41 specified who must list drugs, and the provision is retained in this final rule. Section 207.41(c) now includes more detail about the manner in which drugs manufactured for private label distribution are listed.

(Comment 60) Some comments urged FDA to allow private label distributors to list drugs that are distributed under their names.

(Response) Please see our response to comment 16 regarding the definitions of ''private label distributor'' and ''private label distribution'' in § 207.1 for a discussion of the responsibilities of private label distributors in this final rule. Private label distributors are not obligated—by their status as private label distributors—to register an establishment or list drugs. They may, however, submit drug listing information or establishment registration information if acting as the authorized agent of a registrant on whose behalf the information is submitted.

2. When, after initial registration of an establishment, must drug listing information be submitted? (§ 207.45)

Proposed § 207.45 described an establishment's drug listing obligation at the time of initial registration. It stated that an establishment must, at the time of initial registration, list any drug then being manufactured, repacked, relabeled, or salvaged for commercial distribution at the establishment. Section 207.45 is revised in this final rule to state that such drugs must be listed no later than 3 calendar days after initial registration of the establishment.

(Comment 61) One comment encouraged FDA to provide flexibility in the timing of new drug listing submissions. The comment stated that it supported the current requirement of 5 calendar days from the start of manufacturing.

(Response) Several provisions of this final rule relate to the time periods within which establishment registrations, drug listings, and drug listing updates must be submitted. Section 207.21 states that domestic establishments must register for the first time no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug or an animal feed bearing or containing a new animal drug (whether or not commercially distributed). This 5-day window for initial establishment registration starts at the beginning of manufacture, not the beginning of commercial distribution. Section 207.45 states that each drug being manufactured, repacked, relabeled, or salvaged *for commercial distribution* at the time of initial registration must be listed no later than 3 calendar days after initial registration. Thus, the 3-day window established in § 207.45 relates to those drugs being manufactured at the establishment for commercial distribution at the time of initial registration. We will interpret the phrase ''for commercial distribution'' in § 207.45 flexibly as meaning immediate or near-term commercial distribution, not for storage prior to an initial product launch.

FDA recognizes that because it has made findings that nondisclosure of most drug listing information would be inconsistent with the protection of the public health (see § 207.81), registrants may be reluctant to list drugs that have not yet been commercially launched. FDA intends to interpret the timing requirements in a way that accommodates this concern. FDA also encourages and expects registrants to list drugs promptly upon commercial launch (following § 207.45 or § 207.57 as appropriate), recognizing that manufacturers have an incentive to list drugs promptly and have their proposed NDCs assigned by FDA. After a drug is listed, it should appear in our public NDC database within approximately 1 business day and in our internal database almost immediately.

3. What listing information must a registrant submit for a drug it manufactures? (§ 207.49)

Proposed § 207.49 identified the information that a registrant must provide with a drug listing submission for a drug it manufactures. Section 207.49 is retained and reorganized in this final rule. Some information included in proposed § 207.33(c) (what information must a manufacturer submit before we will assign an NDC number to a drug?) has been incorporated into new § 207.49 as drug listing information because it is not necessary under this final rule for manufacturers to request an NDC from FDA.

(Comment 62) One comment noted that an approved U.S. application

number is included with drug listing information identified in § 207.49 and asked FDA to clarify whether an application must be approved before drug listing information is submitted.

(Response) Section 207.49(a)(7) of this final rule requires registrants to provide the approved U.S. application number with listing information for a drug if one exists. Thus, § 207.49 requires that an approved U.S. application number be provided with drug listing information only if it exists. Unapproved drugs can and must be listed without an application number.

Drugs that are the subject of an application need not be listed until they are manufactured for commercial distribution. Registrants who are awaiting approval of an application may voluntarily reserve an NDC for the drug that is the subject of the application prior to its approval under new § 207.33(d)(3). These registrants are also permitted, but not required, to list a drug before it is marketed, while providing a future start marketing date.

(Comment 63) Many comments opposed the submission of production volume information with drug listing information.

(Response) In the preamble to the proposed rule, FDA stated that it was considering whether to require establishments to provide the number of batches and batch size for each drug subject to the listing requirement that they manufactured, repacked, or relabeled since the establishment last provided listing information (71 FR 51276 at 51312). We have decided not to include such a requirement in this final rule.

(Comment 64) One comment urged FDA to eliminate the requirement that registrants submit representative samples of any other labeling for OTC drug products.

(Response) Section 207.49(a)(14)(ii)(b) of this final rule requires that for each human nonprescription drug not subject to section 505 of the FD&C Act or section 351 of the PHS Act (*i.e.,* not subject to premarket approval), drug listing information include the current label, the package insert (if any), and a representative sampling of any other labeling. The submission of ''any other labeling'' for such drugs is a requirement of section 510(j)(1)(B)(ii) of the FD&C Act.

(Comment 65) One comment questioned the proposed requirement that the ''drug facts'' labeling for OTC drug products be included in drug listing information, arguing that required labeling for OTC products is set forth in OTC monographs and in FDA's regulations in § 201.66.

(Response) We disagree with this comment. Section 207.49(a)(14)(ii)(B) of this final rule requires that labeling submitted with drug listing information for human nonprescription drugs not subject to section 505 of the FD&C Act or section 351 of the PHS Act include the ''content of labeling.'' This term is defined in § 207.1(b) to include, for these drugs, the drug facts labeling required by § 201.66. The submission of drug listing information is the only mechanism by which FDA has quick access to the labeling that is currently in use for marketed OTC drug products. Furthermore, section 510(j)(1)(B)(ii) of the FD&C Act requires that the label, package insert, and a representative sampling of any other labeling be provided with listing information for all such drugs, thus encompassing the drug facts labeling.

(Comment 66) One comment urged FDA to require that drug listing information for human OTC drugs include the current product label, but not other labeling. This comment also urged FDA to accept such labels in portable document format (PDF) files rather than structured product labeling (SPL).

(Response) As explained in response to Comments 64 and 65, the FD&C Act requires that drug listing information for OTC human drugs not subject to section 505 of the FD&C Act or section 351 of the PHS Act include the label, package insert, and a representative sampling of ''any other labeling.'' Therefore, this comment's recommendation that only the current product label (*i.e.,* the container label) be submitted for such products is contrary to the FD&C Act, and we decline to adopt it. Drug listing information is the only mechanism by which FDA collects labeling for such products, and it is important that we have it readily available.

This final rule does not specify a file format for the submission of drug listing information, but it does require electronic submission in a format FDA can ''process, review, and archive.'' (See § 207.61(a) of this final rule.) As explained in our electronic registration and listing guidance, to facilitate the submission of drug establishment registration and drug listing information (including the content of labeling), FDA has adopted the use of extensible markup language (XML) files in a standard SPL format. The automated submission process functions most efficiently and effectively when this information is provided in a standardized format with defined code sets and codes. Information in a properly created and complete SPL file can facilitate processing and allows for greater precision and accuracy through the use of coded data fields rather than merely electronic text. For these reasons, we will continue to expect drug listing information in SPL format.

In the case of unfinished drugs, § 207.49(a)(15)(iv) requires submission of the label (if any) but does not require registrants to submit the content of labeling. Because FDA does not currently electronically process the labels submitted for unfinished drugs, we have accepted and will continue to accept electronic submission unfinished drug labels in JPEG (Joint Photographic Experts Group) file format.

(Comment 67) One comment questioned the proposed requirement that drug listing information include the name of each inactive ingredient in a listed drug. Another comment argued that drug listing submissions for animal drug products in particular should not be required to identify inactive ingredients.

(Response) This requirement is retained in the final rule, specifically in new § 207.49(a)(5), applicable to both human and animal drugs. FDA finds it important to maintain up-to-date inactive ingredient information for all marketed drug products. This allows FDA, for example, to determine the extent to which a particular inactive ingredient is currently in use and identify drug products that contain it. FDA does not have access to this information in the form of a searchable database outside of our drug registration and listing information.

(Comment 68) We received several comments pertaining to the drug listing obligations of contract manufacturers, contract packagers, and contract laboratories. One requested clarification regarding the manner in which a contract manufacturer or packager would submit listing information for an investigational drug manufactured or packaged for use in a clinical trial.

(Response) Contract manufacturers, packagers, and laboratories—unless they are exempt under section 510(g) of the FD&C Act or § 207.13—will generally qualify as manufacturers under this final rule and will be required to register their establishments. Under § 207.41 of this final rule, registrants must list drugs they manufacture, repack, relabel or salvage *for commercial distribution.* The definition of ''commercial distribution in new § 207.1 excludes drugs distributed for investigational use under part 312 (21 CFR part 312) or part 511 (21 CFR part 511). The drugs referred to in this comment may be exempt from listing under this analysis.

(Comment 69) Another comment asked how a contract manufacturer or

packager should be expected to submit twice annual drug listing updates, attesting for example that there have been no changes to a drug's labeling, when the contract manufacturer or packager is not responsible for or aware of labeling changes in the ordinary course of its business.

(Response) This comment relates to a wide variety of situations. We recognize that contractors play an important role in drug manufacture. Some perform specialized operations for another manufacturer (*e.g.,* blister packaging), and others perform all manufacturing operations for a virtual drug company. Some contract manufacturers handle drugs that are the subject of an approved application and are sold under the name of the application holder. Others manufacture OTC drugs for multiple private label distributors. Each situation will require its own analysis under this final rule, and there may be more than one way to satisfy the rule's requirements.

If a contract manufacturer is performing one or more steps in a larger manufacturing operation, it may be shipping an unfinished drug to another contracting party. In that case, the contract manufacturer would submit listing information under § 207.49 for the unfinished drug it distributes commercially, *i.e.,* the unfinished drug that leaves its registered establishment(s). This would include labeling information required under § 207.49(a)(15)(iv), meaning the label applied to the unfinished drug. In this scenario, the contract manufacturer would not be responsible for listing updates that describe labeling changes for the finished drug product, if the contract manufacturer does not commercially distribute the finished drug product.

If a contractor is performing all steps or just the final steps in a drug manufacturing process, the contractor should describe the finished drug product in its listing submission. In some cases, a contract manufacturer may be responsible for formulating the product and developing its labeling. This might be true in the case of an OTC store brand, private label distribution product, for example. In that situation, the contracting parties would likely agree that the contract manufacturer is in the best position to submit drug listing information and updates (as it is required to do under this final rule), and this would include the submission of any labeling changes with twice annual listing updates. In other cases, a contractor might play a much smaller role. It might only place a product manufactured and developed by someone else into its final packaging. In that case, the contractor would be required by this final rule to submit listing information pertaining to the finished drug product, including the twice annual updates. The contractor might satisfy this obligation by consulting with the drug's developer about any changes in drug listing information or by letting the drug's developer act as its authorized agent for the submission of drug listing information and updates. At all times, however, the actual manufacturer of a drug (or repacker, relabeler, or salvager) is legally responsible for ensuring that the requirements of this final rule are satisfied.

(Comment 70) One comment stated that ''the proposed requirement for finished product contract testing laboratories to list all of the products they test should be eliminated.'' The comment pointed out that testing laboratories only handle representative samples of products that do not enter the supply chain.

(Response) This comment addresses an issue that arises under the FD&C Act and the drug registration and listing regulations as they have long existed. (See the definition of ''manufacturing or processing'' that has existed in § 207.3 prior to this final rule.) Testing laboratories, whether they test finished drug products or in-process materials, may have important roles in drug manufacturing and are appropriately treated as manufacturers under part 207 if they engage in testing or control procedures necessary for manufacture under current good manufacturing practices. Any testing laboratory that qualifies as a ''manufacturer'' under this final rule must register its establishment(s) where drugs are tested. The listing obligation, however, applies only to drugs that a registrant places into commercial distribution. Therefore, if a laboratory tests in-process materials or finished product and then commercially distributes the tested product, *e.g.,* for further processing or for distribution as finished product, that laboratory would have an obligation to list the drugs it commercially distributes. More likely, however, if the laboratory merely tests product samples and reports the test results to another party without further distributing the tested samples, it has no listing obligation.

(Comment 71) One comment expressed concern that importers would have to identify manufacturers for their drug components and provide a chain of custody description for each handler from manufacturer to importer.

(Response) This comment reflects a misunderstanding of a statement in the proposed rule describing section 801(d)(3) of the FD&C Act. To clarify, § 207.49(a)(12) of this final rule requires a registrant listing a drug it manufacturers to provide: (1) The name and UFI of the establishment where the registrant manufactures the drug and (2) the name and UFI of every other establishment where manufacturing is performed for the drug. With respect to this second category of information, if the registrant provides a properly assigned and listed NDC for unfinished drug(s) it uses to produce the listed drug (sometimes referred to as ''immediate source NDCs''), the registrant does not need to provide names and UFIs of the upstream establishments.

(Comment 72) One comment asked FDA to clarify a statement in the preamble of the proposed rule regarding certificates of analysis for imported articles.

(Response) This comment reflects a misunderstanding of the proposed rule. The passage it refers to quotes section 801(d)(3) of the FD&C Act (71 FR 51276 at 51284). Section 801(d)(3) of the FD&C Act applies only to certain imported products, and this final rule does not implement it.

4. What listing information must a registrant submit for a drug it repacks or relabels? (§ 207.53)

Proposed § 207.53 identified the information that a registrant must provide with a listing submission for a drug it repacks or relabels. Section 207.53 is retained and reorganized in this final rule. Some information included in proposed § 207.33(d) (What information must a repacker or relabeler submit before we will assign an NDC number to a drug?) has been incorporated into new § 207.53 as drug listing information because it is not necessary under this final rule for manufacturers to request an NDC from FDA.

(Comment 73) A comment from the medical gas industry expressed concern about the proposed rule's requirement that repackers identify, in drug listing information, the NDC associated with a drug immediately before it is received by the repacker for repackaging. This comment argued that the complexity of medical gas distribution makes this requirement difficult to satisfy.

(Response) We agree that medical gas repackers would need to significantly change the way they currently do business to identify immediate source NDCs as specified in the proposed rule. In response to this comment, we have included an exception in § 207.53 of

this final rule so that repackers and relabelers of medical gases are not required to include with drug listing submissions the NDC assigned to each medical gas they receive for repacking or relabeling.

5. What are the requirements for reviewing and updating listing information? (§ 207.57)

Proposed § 207.57 described the requirements for reviewing and updating drug listing information. The provision is retained in this final rule with editorial revisions intended to improve clarity. Additionally, the section now says registrants are encouraged to submit listing updates at the time of any change affecting previously submitted information. We have also deleted a reference to § 207.55. Under § 207.55, FDA may ask a registrant to explain the basis for its belief that a drug is not subject to approval. We do not expect registrants to routinely update information provided to us under § 207.55.

(Comment 74) Some comments opposed the requirement that to satisfy the June and December listing update obligation, registrants must certify that no changes have occurred if no changes have occurred since the last review and update of listing information.

(Response) The preamble to the proposed rule specifically requested comments regarding the burden that may result from the no changes certification requirement in the context of drug listing updates (71 FR 51276 at 51314). We have retained in this final rule the requirement in § 207.57(b) that registrants update their submitted drug listing information each June and December. The review and updating of drug listing information is critical to the integrity of FDA's database. We recognize, however, that requiring registrants to submit a twice-annual ''no changes'' certification, on a product-by-product basis, for each of their listings would impose a substantial burden on registrants, particularly those that maintain hundreds or thousands of drug listings. Therefore, § 207.57 of this final rule requires registrants to report changes to drug listing information either at the time of any change affecting information previously reported or during the next June or December listing update following the change. At the time of the annual registration update under § 207.29(b), a registrant may submit a blanket ''no changes'' certification covering all of its listed drug products for which no changes affecting previously reported listing information were made since the last annual registration update or listing submission. This blanket, ''no changes'' certification applies only to drug listing information that has been submitted electronically, as it would be too burdensome for FDA to maintain certifications for information that has not been submitted electronically. Therefore, it cannot be used to report that drug listing information submitted on paper in the past remains current. This limitation is intended to ease FDA's administrative burden and allow FDA to consider drug listing information to be fully migrated from paper submissions to our electronic drug registration and listing system.

Please see our response to Comment 30, which addresses this issue in the context of establishment registration updates.

(Comment 75) One comment stated that the obligation to provide updates on individual drug listings within 30 days will demand a great deal of resources from manufacturers.

(Response) This comment did not cite the specific provision of the proposed rule at issue. The preamble to the proposed rule acknowledged that proposed § 207.57(b) would require that drug listing information be reviewed and updated only every June and December, but also stated that FDA would request updates to listing information within 30 calendar days of a change, to maintain the accuracy of our drug listing database (71 FR 51276 at 51314). Under § 207.57 of this final rule, registrants are encouraged to submit updated drug listing information at the time of any change affecting information previously submitted, but they are required to submit such information only every June and December.

(Comment 76) Two comments asked FDA to clarify whether a registrant may report all changes to drug listing information when they occur, *i.e.,* on a rolling basis, instead of conducting a review and update each June and December.

(Response) Under § 207.57 of this final rule, registrants must review and update their drug listing information each June and December. This is a requirement of section 510(j)(2) of the FD&C Act. Registrants are additionally encouraged, but not required, to update drug listing information at the time when changes are made to previously reported information. These updates do not, however, take the place of the June and December updates, which may be satisfied by a no changes certification if no changes have occurred since the last review and update. We will read ''since the last review and update'' in § 207.57(b)(2) as referring to the registrant's most recent listing update for a given drug, whether submitted in June, December, or at any other time.

(Comment 77) One comment encouraged FDA to codify a registrant's ability to submit updated listing information at the time a change is made, rather than waiting for the next June or December review and update. This comment referred to a statement in the preamble to the proposed rule stating that registrants are requested to submit listing information within 30 days of a change.

(Response) We agree with this comment and have revised § 207.57 accordingly. New § 207.57 states that registrants are encouraged to submit listing updates at the time of any change affecting information previously submitted. This provision of the final rule does not refer to a 30-day window for such listing updates. We intend to read ''at the time of any change'' flexibly, encouraging registrants to submit listing updates as soon as possible, but allowing such updates at any time before they are due at the next June or December review and update.

(Comment 78) One comment expressed concern regarding the manner in which a drug's discontinuation is to be reported under § 207.57. This comment noted that historically, many registrants have waited to report that a drug has been discontinued until they no longer have to report the drug under applicable agreements with the Centers for Medicare and Medicaid Services. According to this comment, if an NDC is identified as discontinued while the drug is still in distribution up until expiration, there may be problems related to reimbursement and other matters.

(Response) The FD&C Act and § 207.57 of this final rule require listing updates, including information that a drug has been discontinued, at the latest, at the time of the next June or December review and update following the discontinuation. In the case of drugs that are subject to part 314, § 314.81(b)(3)(iv) also requires that their withdrawal from sale be reported to FDA. The reporting deadline under § 314.81(b)(3)(iv) is within 15 working days of the withdrawal from sale before the effective date of this final rule and within 30 calendar days of the withdrawal from sale after the effective date of this final rule. It is important that FDA receive this information soon after discontinuation for the integrity of our database.

In this final rule, as in the proposed rule, § 207.57 requires registrants, when reporting that a listed drug has been discontinued, to provide the expiration

date of the last lot manufactured, repacked, relabeled, or salvaged. FDA regards this date as the ''end marketing date'' and includes it in the public NDC database when a drug is reported to be discontinued.

Please note that, in addition to the requirements just discussed, section 506C of the FD&C Act, as amended by FDASIA, requires manufacturers of certain drugs that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, to notify FDA of a permanent discontinuance or certain interruptions in manufacture at least 6 months prior to the date of discontinuance or interruption or as soon as practicable if 6-month's prior notice is not possible.

(Comment 79) Two comments opposed the requirement in § 207.57 that registrants provide, for a discontinued drug, the expiration date of the last lot manufactured, repacked, relabeled, or salvaged, arguing that the expiration date of the last lot provides no assurance that the drug product will be available to consumers until that date is reached.

(Response) As explained in response to Comment 78, our use of the expiration date of the last lot as an ''end marketing date'' facilitates reimbursement while remaining stock of a discontinued drug works its way through distribution.

(Comment 80) Two comments requested clarification regarding how the inclusion of an approved application number in a drug listing submission can take the place of the content of labeling in SPL format, specifically how updated labeling would be provided at the time of a listing update if only the application number is referenced.

(Response) The proposed rule indicated that if ''a manufacturer provides a drug's approved U.S. application number as part of a drug's listing information, the labeling required under proposed § 207.49(g)(1) and . . . 207.49(g)(2) would be deemed to accompany the listing information'' (71 FR 51276 at 51309). This was written prior to FDA's adoption of SPL as the submission standard and is not an accurate reflection of how the process operates today. However, FDA has considered how our electronic system can avoid unnecessary duplication of effort between the submission of labeling updates to applications and the submission of drug listing information.

Under this final rule, a drug listing submission, whether it includes an approved application number or not, must include content of labeling as specified in § 207.49. An advantage of the SPL format is that it allows the holder of a newly approved application to submit the content of labeling once, satisfying its obligations under parts 314 and 207 in a single submission. Upon initial approval, an applicant is required to submit a copy of final approved labeling. An electronic drug listing submission that includes the content of labeling in SPL format can satisfy this obligation. Even if the drug product is not yet ready for commercial distribution upon approval, SPL allows for a future start marketing date in the listing information so that a second submission is not necessary when the product is commercially launched.

As discussed in response to Comment 15, most drug labeling changes necessitate a listing update under § 207.57 of this final rule. Registrants who submit drug listing information through FDA's CDER Direct electronic submission portal (as well as those using some commercial software) will be able to recall a previous submission, including the content of labeling, and make appropriate changes when a listing update is due. But reference to an application number alone will not satisfy the requirement that updated content of labeling be submitted under § 207.57 in this final rule.

F. Electronic Format for Registration and Listing (Part 207, Subpart E)

Proposed § 207.61 stated that establishment registration and listing information must be submitted to FDA electronically. As proposed, § 207.61 would have allowed advertisements and some labeling to be submitted to FDA either in paper or electronic format. In this final rule, § 207.61 is revised for clarity. Additionally, the final version of § 207.61 requires electronic submission of all establishment registration and listing information, consistent with FDAAA (no longer allowing for the submission of advertising on paper), unless a waiver is granted, and states that FDA may issue guidance from time to time on how to provide information in electronic format. Because the SPL format currently used for electronic submission of registration and listing information does not accommodate the submission of drug advertising, taking into account various types of advertising media currently in use, FDA is not currently collecting advertisements as part of drug listing information. If this technical limitation is resolved, we will explain in future guidance how and what registrants should transmit electronically as a representative sampling of advertisements. In the meantime, we may ask individual registrants to submit a representative sampling of advertisements for specific prescription human drug products not subject to section 505 of the FD&C Act, relying on our authority under section 510(j)(1)(B)(i) of the FD&C Act and § 207.49(a)(14) of this final rule.

The final version of § 207.61 also clarifies that, while drug registration and listing information must generally be submitted in the English language, in some cases the content of labeling may be submitted in a foreign language along with an accurate English translation.

(Comment 81) One comment stated that information should be included in the final rule to address whether FDA intends to develop a separate database for animal health products or incorporate animal drugs into the proposed electronic drug registration and listing database. The comment recommended that if a separate database is planned, information on whether the same data elements will be required to obtain an NDC number and list products would be helpful.

(Response) At issue in this rulemaking are changes to FDA's regulations governing drug establishment registration and listing, *i.e.,* changes to the codified language presented in the proposed rule and in this final rule. These regulations do not describe the electronic drug registration and listing systems developed by FDA, which may change from time to time. Currently, FDA maintains separate electronic systems for establishment registration and listing for human drugs and for animal drugs. The information that must be submitted with a drug listing submission, for both human drugs and animal drugs, is described in the regulations codified in part 207 as amended by this final rule.

(Comment 82) One comment noted that at the time of the proposed rule and the comment period, FDA's electronic drug registration and listing system had yet to be developed. Accordingly, stakeholders were unable to comment on an electronic system that had yet to be developed.

(Response) We understand stakeholder interest in the development of our electronic system for drug registration and listing. As noted in response to Comment 81, however, the amended regulations adopted in this rulemaking do not describe the electronic drug registration and listing systems developed by FDA. They generally describe information that must be submitted to FDA, and they require that it be submitted electronically. Therefore, the proposed rule did not solicit comments on the electronic drug

registration and listing system then under development.

After the proposed rule was published, Congress amended the FD&C Act to require electronic submission of drug establishment registration and listing information. To implement this statutory change, FDA published draft guidance in 2008 and final guidance in 2009 concerning electronic submission of drug establishment registration and listing information. Stakeholders had an opportunity to comment on the electronic system described in our draft guidance and, as with all FDA guidance, have an ongoing opportunity to comment at any time.

FDA currently accepts drug establishment registration and drug listing information submitted electronically. We expect registrants to find electronic submission less burdensome than the use of paper forms, and we accept comments and suggestions from stakeholders regarding improvements to our electronic submission systems.

(Comment 83) One comment recommended that to facilitate the annual review and updating of both establishment registration and drug listing information, FDA provide registrants with a report of their current registration and listing information.

(Response) This comment does not relate to language that would be included in the codified portion of this final rule, but it does raise an important issue we would like to address. At all times, registrants are responsible for keeping track of registration and listing information they have submitted to FDA and should ensure the information is securely stored and can be retrieved.

Registrants who use an agent to submit establishment registration and drug listing information to FDA are encouraged to maintain their own records of the submitted information or obtain assurances that the agent will do so and will make the information available to the registrant on request, including if their business relationship is terminated.

FDA currently maintains publicly searchable databases that can be used to confirm an establishment is registered. Information about registered blood establishments is available through FDA's electronic Blood Establishment Registration (eBER) public query application. Information about registered HCT/P establishments is available through the Human Cell and Tissue Establishment Registration (HCTERS) public query application. Information about registered drug establishments can be obtained through FDA's Drug Establishments Current Registration Site (DECRS). Additionally, FDA's NDC Directory currently includes listed finished drug products, but not unfinished drug products. It may be expanded in the future to include all listed drugs. Registrants can check these sources and may also request a report of their own registration and listing information from CDER's Drug Registration and Listing staff.

(Comment 84) Comments noted that changes to part 11 (21 CFR part 11) are being considered by the Agency and recommended that electronic submission of drug registration and listing information be delayed or exempt from compliance with part 11 until these changes have been decided.

(Response) Because of changes to section 510(p) of the FD&C Act adopted in FDAAA, registration and listing information is currently submitted electronically. Exceptions from the electronic submission requirement will be handled in accordance with the waiver provisions in this final rule (§§ 207.65, 607.22, and 1271.23).

Part 11 sets forth criteria under which FDA considers electronic records and signatures to be trustworthy and reliable. Part 11 applies to electronic records that are created, modified, maintained, archived, retrieved, or transmitted under statutory and regulatory requirements. In 2003, FDA published guidance for industry titled ''Part 11, Electronic Records; Electronic Signatures—Scope and Application'' (2003 Part 11 Guidance, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) and announced its availability in the **Federal Register** (68 FR 52779, September 5, 2003). This guidance announced a reexamination of part 11, a narrow interpretation of its scope, and a policy of enforcement discretion with respect to certain of its requirements. Part 11 currently remains in effect, and FDA's policy of enforcement discretion applies as described in the guidance.

Against this backdrop, the proposed rule included a discussion of how FDA intended to apply part 11 to electronic drug registration and listing. (See 71 FR 51276 at 51317.) Proposed §§ 207.61, 607.22, and 1271.22 specified that certain requirements of part 11 would not apply to information submitted to FDA under parts 207, 607, and 1271. In § 207.61 of this final rule, the applicability of part 11 is stated as follows: The submission of advertisements and labeling is exempt from the requirements of § 11.10(a), (c) through (h), and (k) and the corresponding requirements of § 11.30. Other information submitted under part 207, as well as information submitted under parts 607 and 1271, is exempt from the requirements of § 11.10(b), (c), and (e) and the corresponding requirements of § 11.30. These statements in the codified portion of this final rule are intended to be read together with any current FDA guidance concerning our enforcement of part 11. For example, FDA's 2003 Part 11 Guidance states that we do not intend to take action to enforce compliance with the validation and audit trail requirements of part 11. This includes requirements described in § 11.10(a) and (e). Until our 2003 Part 11 Guidance is withdrawn or modified, these statements regarding enforcement discretion remain current. Therefore, any person submitting information electronically to FDA under this final rule may rely on the exemptions from part 11 written into parts 207, 607, and 1271, in addition to statements regarding part 11 enforcement discretion in current FDA guidance.

(Comment 85) One comment noted that a citizen petition is currently pending before FDA requesting that part 11 be revoked in its entirety (Docket No. FDA–2004–P–0036, formerly Docket No. 2004P–0429/CP1). This comment asked FDA to respond to the citizen petition before it completes this rulemaking.

(Response) The referenced citizen petition remains under review, and the part 11 regulations are currently being implemented as explained in FDA's 2003 Part 11 Guidance. FDA's publication of this final rule should not be interpreted as providing any indication of the manner in which the citizen petition will be resolved.

G. Miscellaneous (Part 207, Subpart F)

Section 207.81 of the proposed rule identified establishment registration and listing information that will be available or not available for public disclosure after it is submitted to FDA. Section 510(f) of the FD&C Act states that establishment registration information is available for inspection and drug listing information is generally not available for inspection unless the Secretary (by delegation FDA) finds that an exemption from disclosure would be inconsistent with protection of the public health. Consistent with this statutory provision, proposed § 207.81 stated that establishment registration information would be generally available for disclosure and that most, but not all, drug listing information would be available for disclosure, as its nondisclosure would be inconsistent with protection of the public health. Generally categorized as not available for disclosure in the proposed rule was information obtained under:

- Proposed § 207.33(d)(1)(ii)—Source NDCs for repacked or relabeled drugs submitted in the context of an NDC request for such drugs,
- Proposed § 207.54(b)(1)—Source NDCs for salvaged drugs, and
- Information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505 or 512 of the FD&C Act, the premarket approval requirement for new drugs and new animal drugs.

In this final rule, § 207.81 has been revised in several ways. The section has been reorganized so that registration and listing information that will be available for public disclosure is identified in paragraph (a), and exceptions are identified in paragraphs (b) and (c). Cited section numbers have been revised, consistent with the renumbering of sections in this final rule (and the shifting of some information required in the proposed rule as supporting an NDC request to information required in the final rule as drug listing information). Substantively, § 207.81 of this final rule identifies an expanded set of information obtained under the following sections as information that will not be available for public disclosure:

- § 207.53(b)—Immediate source NDCs for repacked or relabeled drugs;
- § 207.54(a)—Immediate source NDCs for salvaged drugs;
- § 207.54(c)—The name or UFI of an establishment where a specific drug is salvaged;
- § 207.55—Information submitted as the basis upon which it has been determined that a particular drug is not subject to section 505 or 512 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act;
- § 207.33(d)(3)—Information submitted to reserve an NDC;
- § 207.49(a)(9)—For unfinished drugs, the number assigned to the Drug Master File or Veterinary Master File, if any;
- § 207.49(a)(12)—The names and UFIs of establishments where manufacturing is performed for listed drugs and/or immediate source NDCs;
- § 207.53(c)—The names and UFIs of establishments where repacking or relabeling is performed for listed drugs; and
- § 207.49(a)(5)—The names of any inactive ingredients submitted with drug listing information for which the registrant makes a valid assertion of confidentiality.

In this final rule, establishment registration information will be available for disclosure, consistent with section 510(f) of the FD&C Act, except in limited circumstances as described in § 207.81(c). FDA has found that nondisclosure of most drug listing information for marketed drugs would be inconsistent with the protection of the public health. In most cases, drug listing information is obvious or is disclosed elsewhere (*e.g.,* a drug's established and proprietary names, its dosage form and route of administration, its active ingredient(s)). Specifically, FDA has made a finding that nondisclosure of the listing information identified in the following bulleted list would be inconsistent with protection of the public health, except in limited circumstances as described in § 207.81(c):

- Information obtained under § 207.33 will be available for public disclosure, but only after a drug is marketed. This information that will be available for public disclosure includes information a registrant or private label distributor submits or updates under § 207.33(c) to obtain an NDC labeler code but does not include information submitted under § 207.33(d)(3) to reserve an NDC. Information submitted under § 207.33(c) to obtain a labeler code (and updates to the information) includes basic contact information for the registrant or private label distributor to whom the labeler code is assigned, the types of activities (*e.g.,* manufacture, repackaging, or private label distribution) in which the person requesting the labeler code engages with respect to drugs, and the types of drugs to which the labeler code will be applied. This is not necessarily, but is arguably, classified as drug listing information because it relates to NDCs and labeler code segments of NDCs. FDA makes the finding referred to in section 510(f) of the FD&C Act that nondisclosure of this information, in the case of marketed drugs, would be inconsistent with protection of the public health. The contact information described in § 207.33(c)(1)(i) allows consumers to verify in some cases that they do not have a counterfeit product. It also provides additional contact information for the consumer's reference. Disclosure of the types of activities reported under § 207.33(c)(1)(ii) may provide additional clarity as to a labeler's role in producing or marketing a drug. Information on the types of drugs to which a labeler code will be applied, described in § 207.33(c)(1)(iii), is largely available to the public, but centralizing it promotes the free flow of information to interested consumers.
- Most information obtained under § 207.49 (listing information a registrant must submit for a drug it manufactures) will be available for public disclosure after a drug is marketed. This information includes the drug's NDC; its established and proprietary name; the name and quantity of each active pharmaceutical ingredient in the drug; the name of each inactive ingredient (unless a valid assertion of confidentiality is made); the dosage form; the drug's approved U.S. application number if any; the drug type (finished vs. unfinished, human vs. animal, prescription vs. nonprescription); for drugs subject to the imprinting requirements of 21 CFR part 206, the drug's size, shape, color, scoring, and code imprint (if any); the route or routes of administration of the drug; the schedule of the drug under the Controlled Substances Act; advertisements; labeling; contact information for private label distributors; OTC monograph references if any; and the date on which a drug was introduced into commercial distribution. FDA makes the finding referred to in section 510(f) of the FD&C Act that nondisclosure of the foregoing information, in the case of marketed drugs, would be inconsistent with protection of the public health. The drug information described in §§ 207.49(a)(1), (3), (10), (15), and 207.49(b)(1) and (2) will enable individuals with concerns about counterfeiting to compare information about a product in their possession with information provided to FDA. The ingredient information described in §§ 207.49(a)(4) and (5) will in some cases allow individuals to verify ingredient information provided in labeling against FDA's records. The information described in §§ 207.49(a)(6), (8), and (11) relates to proper physical form and use of a drug. The application number described in § 207.49(a)(7) allows individuals to access disclosable FDA records about a drug's approval. Whether and how a drug is scheduled under the Controlled Substances Act (§ 207.49(a)(13)) relates to safe use of the drug. The advertisements and labeling described in §§ 207.49(a)(14) and (15) may include information individuals have not seen elsewhere describing the risks and benefits of a drug. Furthermore, FDA's disclosure of labeling information obtained under § 207.49(a)(15) will allow for the availability of current drug labeling information through DailyMed, a computerized repository of drug information maintained by the National Library of Medicine. The contact information described in § 207.49(a)(16)(ii) may provide additional contact information for an

individual's reference. All of this information is largely available to the public, but centralizing it promotes the free flow of information to interested consumers, health care providers, and others. Note that two types of information obtained under § 207.49 will not be available for public disclosure: (1) The names of inactive ingredients in a listed drug if the registrant listing the drug makes a valid assertion of confidentiality for them at the time of drug listing and (2) the number assigned to the Drug Master File or Veterinary Master File, if any, that describes the manufacture of an unfinished drug.

- Most information obtained under § 207.53 (listing information a registrant must submit for a drug that it repacks or relabels) will be available for public disclosure after a drug is marketed. This information includes the repacked or relabeled drug's NDC, labeling, advertisements, and contact information for private label distributors. FDA makes the finding referred to in section 510(f) of the FD&C Act that nondisclosure of the foregoing information, in the case of marketed drugs, would be inconsistent with protection of the public health. The NDC described in § 207.53(a) helps identify who repacked or relabeled a drug. Labeling and advertising information described in §§ 207.53(d) and 207.53(e) may include information individuals have not seen elsewhere describing the risks and benefits of a drug. Furthermore, FDA's disclosure of labeling information obtained under § 207.53(d) will allow for the availability of current drug labeling information through DailyMed, a computerized repository of drug information maintained by the National Library of Medicine. The contact information for private label distributors described in § 207.53(f)(2) may provide additional contact information for an individual's reference. All of this information is largely available to the public, but centralizing it will promote the free flow of information. Note that two types of information obtained under § 207.53 are not available for disclosure: (1) The NDC assigned to a finished drug received by a registrant for repacking or relabeling and (2) the name and UFI of establishments where repacking or relabeling is performed.
- Some information obtained under § 207.54 (listing information a registrant must submit for a drug it salvages) will be available for public disclosure after a drug is marketed. This information includes the salvaged drug's lot number and expiration date. FDA makes the finding referred to in section 510(f) of the FD&C Act that nondisclosure of the foregoing information, in the case of marketed drugs, would be inconsistent with protection of the public health. Disclosure of the lot number and expiration date information described in § 207.54(b) may help address any concerns about a salvaged product's quality, potency, and shelf life.
- Most information obtained under § 207.57 (information registrants must submit when updating listing information) will be available for public disclosure. In most cases, information submitted under § 207.57 updates information previously submitted under §§ 207.49, 207.53, or 207.54. The same disclosure rules will apply whether information is submitted in an original drug listing submission or in an updated listing. Our findings under section 510(f) of the FD&C Act, described previously, that nondisclosure of certain listing information obtained under §§ 207.49, 207.53, and 207.54 would be inconsistent with protection of the public health apply whether the information is obtained in an original listing submission or an updated listing submission. Accordingly, the reasons supporting this finding discussed previously apply to updates submitted under § 207.57. Some information obtained under § 207.57 will not have been received previously under §§ 207.49, 207.53, or 207.54. This information includes: (1) The date a registrant discontinues the manufacture, repacking, relabeling, or salvaging for commercial distribution of a listed drug and the expiration date of the last lot manufactured, repacked, relabeled, or salvaged, (2) the date a registrant resumes the manufacture, repacking, or relabeling, for commercial distribution or a drug previously discontinued, and (3) certifications that no changes have occurred since the last listing review and update. FDA makes the finding referred to in section 510(f) of the FD&C Act that nondisclosure of the foregoing information, in the case of marketed or discontinued drugs, would be inconsistent with protection of the public health. The date a business discontinues or resumes manufacturing a drug, submitted under § 207.57(b)(1)(ii) or (iii), may help address concerns some individuals may have about whether a drug in their possession is counterfeit. The certification that no changes have occurred described in § 207.57(b)(2) will inform individuals that drug listing information previously submitted to FDA is up to date as of the no changes certification date.

(Comment 86) One comment requested that FDA not disclose the names of inactive ingredients in animal drugs submitted with drug listing information. This comment stated that inactive ingredients in animal drugs are generally not listed on labels. Another comment urged FDA not to place the burden on registrants to proactively request that the names of inactive ingredients in human drugs be treated as trade secrets.

(Response) The proposed rule included a discussion about disclosure of inactive ingredients reported in drug listing submissions and stated that FDA will disclose this information unless it is subject to trade secret protection. See 71 FR 51276 at 51321. In this final rule, we are codifying that approach by making it clear in § 207.81 that we will not disclose the names of any inactive ingredients submitted with drug listing information for which the registrant makes a valid assertion of confidentiality under § 20.61 or other applicable provision of law.

This approach will apply to both human and animal drugs in an ingredient-specific way. In other words, in the absence of a well-supported assertion of confidentiality for any given inactive ingredient reported under § 207.49, the name of that inactive ingredient will be available for public disclosure. The inactive ingredient composition of a drug product is of interest to consumers and in most cases is already disclosed on drug labels. We find that categorical nondisclosure of inactive ingredient information would be inconsistent with protection of the public health. It is therefore appropriate that FDA consider this information disclosable in the absence of a valid assertion of confidentiality that supports nondisclosure.

(Comment 87) One comment urged FDA not to disclose the relationship between customs brokers and their clients. This comment noted that the proposed rule would have required foreign establishments to identify in their establishment registrations each person who imports or offers for import their drugs into the United States. The proposed rule would have defined the term ''person who imports or offers for import'' broadly to include agents and brokers. As with establishment registration information generally, this information would have been available for disclosure under § 207.81 of the proposed rule.

(Response) As explained in our response to comment 11, in this final rule, we define the term ''person who imports or offers for import'' more narrowly than it was defined in the proposed rule. The new definition is not intended to include persons operating

merely as customs brokers. Therefore, a person operating merely as a customs broker will not be identified in a foreign establishment's registration information and hence will not have its relationship with the foreign establishment disclosed under § 207.81.

(Comment 88) One comment asked FDA to clarify the confidentiality of information submitted to obtain an NDC. Several comments stated that disclosure of listing information is inappropriate for a yet-to-be approved product.

(Response) As discussed in response to comment 31, under this final rule, registrants will propose their own NDCs with drug listing submissions. It is not necessary under this final rule to request an NDC from FDA and support that request with the information specified in § 207.33(c) of the proposed rule. Some of the information specified in proposed § 207.33(c) (*e.g.,* the drug's proprietary name and established name) has been added to drug listing information required under §§ 207.49, 207.53, and 207.54 of this final rule. The foregoing discussion explains which drug listing information will be available for disclosure and that it will not be available for disclosure until after the drug is marketed.

Section 207.33(d)(3) of this final rule allows anyone with a labeler code to voluntarily reserve an NDC for a drug product under development before it is listed. Information submitted under § 207.33(d)(3) to reserve an NDC is identified in § 207.81(b)(3) as generally exempt from disclosure. Because information submitted to FDA under § 207.33(d)(3) will relate to drug products under development, this exemption from disclosure prior to marketing is not inconsistent with protection of the public health.

(Comment 89) Two comments stated that under the proposed rule, drug listing information would be exempt from public disclosure unless the Secretary deemed its release to be necessary. These comments asked FDA to clarify the circumstances under which disclosure of drug listing information would be considered necessary.

(Response) These comments reflect a misunderstanding of the proposed rule. In the proposed rule, § 207.81 stated unambiguously that ''[a]fter a drug is listed, all information obtained for that drug under §§ 207.33, 207.49, 207.53, and 207.54,'' except for stated exceptions, would be made available for public disclosure upon request or at FDA's discretion (71 FR 51276 at 51353). We have determined, under section 510(f) of the FD&C Act and as explained in the foregoing discussion, that most drug listing information relating to marketed products will be categorically presumed to be available for public disclosure because an exemption from disclosure would be inconsistent with protection of the public health. In the foregoing discussion, we have explained that § 207.81 of this final rule identifies a set of drug listing information that will generally not be available for public disclosure.

(Comment 90) One comment urged FDA not to disclose registration and listing information that reveals business relationships among trading partners, such as those between a drug's manufacturer and a private label distributor or between a manufacturer and a retail service repackager.

(Response) We have carefully considered this comment, along with section 510(f) of the FD&C Act and our longstanding rules and policies regarding disclosure of registration and listing information. As a statutory matter, establishment registration information is generally disclosable. (See section 510(f) of the FD&C Act.) Thus, information required for establishment registration under § 207.25 of this final rule is disclosable.

This final rule requires that foreign establishments report the name of each importer known to the establishment and the name of each person who imports or offers to import its drugs into the United States. This information is treated as establishment registration information under section 510(i) of the FD&C Act and under § 207.25 of this final rule, rather than as drug listing information. Because the information is establishment registration information, both the FD&C Act and this final rule require that it be available for public disclosure. FDA's intention to make this information available for disclosure was highlighted in the proposed rule (71 FR 51276 at 51321).

Drug listing information will not be available for public disclosure under this final rule unless its nondisclosure would be inconsistent with protection of the public health, as set forth in section 510(f) of the FD&C Act. Most drug listing information is obvious or is disclosed elsewhere such as in labeling (*e.g.,* size, shape, color, scoring, route of administration, approved application number, active ingredient(s)) and its nondisclosure would be inconsistent with protection of the public health. However, we recognize that, as emphasized in this comment, some drug listing information may reveal confidential business relationships. This final rule exempts from public disclosure drug listing information obtained under § 207.49(a)(12) (name and UFI of the establishments where a drug is manufactured and/or immediate source NDCs), § 207.53(c) (name and UFI of establishments where repacking or relabeling is performed), or § 207.54(c) (name and UFI of establishments where salvaging is performed).

(Comment 91) One comment urged FDA to treat all registration and listing information as categorically exempt from disclosure.

(Response) We decline to take this approach. As explained in the foregoing discussion, the disclosure provisions in this final rule are consistent with section 510(f) of the FD&C Act, notably its requirement that establishment registration information be made publicly available and that drug listing information be disclosed only to the extent that its nondisclosure would be inconsistent with protection of the public health.

H. Human Cells, Tissues, and Cellular and Tissue-Based Products (Part 1271)

The proposed rule included relatively minor amendments to part 1271 to require electronic submission of establishment registration and listing information for HCT/Ps. These amendments are retained in this final rule with some revisions. Under this final rule, manufacturers of HCT/Ps that are regulated solely under section 361 of the PHS Act are subject to establishment registration and listing under part 1271. Manufacturers of HCT/Ps that are regulated under section 351 of the PHS Act or as drugs under section 505 of the FD&C Act are subject to establishment registration and listing under part 207. (HCT/Ps that are regulated as medical devices under the FD&C Act are subject to establishment registration and listing under part 807.)

(Comment 92) One comment was concerned about the breadth of the definition of ''importer'' in proposed § 1271.3(mm). This comment noted that the proposed rule's definition of ''importer'' appeared to include domestic transplant centers (hospitals) housing patients awaiting hematopoietic stem cell (HSC) transplant and argued that requiring foreign establishments to identify such hospitals as ''importers'' would be unreasonably burdensome.

(Response) Please see our response to Comment 9 regarding the definition of ''importer'' in § 207.1. We agree with those comments that challenged the proposed definition as too broad, particularly as it would have captured downstream recipients of imported products. In parts 207, 607, and 1271,

we have narrowed the new definitions of ''importer'' by adding the words ''at the time of entry.'' Therefore, these definitions no longer capture downstream recipients such as hospitals.

IV. Compliance Dates

This final rule is effective November 29, 2016.

The proposed rule included proposed compliance dates by which registrants and other affected persons would be required to comply with different aspects of a final rule. For example, we proposed that manufacturers, repackers, and relabelers be given 3 years from the effective date of a final rule to ensure that the appropriate NDC appear on their labels. Proposed compliance deadlines were set forth in the preamble to the proposed rule but were not reflected in proposed codified regulatory language. (See 71 FR 51276 at 51345.)

The compliance dates are adjusted in this final rule to account for changes we have made in the final rule and to account for our 2009 implementation of electronic registration and listing under part 207 in accordance with revisions to the FD&C Act. Compliance dates associated with this final rule are presented in table 2.

Registrants are encouraged to comply with this final rule as soon as possible after its effective date. In many cases, the final rule will not necessitate changes in a registrant's current registration and listing practices because electronic submission of registration and listing information already takes place, and the information currently collected generally comports with this final rule. We recognize, however, that this final rule introduces new requirements, and some registrants will need to adjust their registration and listing activities. Table 2 should be read as a statement that FDA intends to exercise enforcement discretion between the effective date of this final rule and the compliance deadlines set forth in the table with respect to changes introduced in this final rule. At all times, however, persons subject to registration and listing must fulfill their statutory obligations and the relevant regulatory provisions set forth in parts 207, 607, and 1271, either before or after the effective date of this final rule.

TABLE 2—COMPLIANCE DEADLINES

Requirement	Effective date or compliance deadline
Effective date of the final rule	90 days after publication.
Electronic submission of establishment registration and listing information under amended part 207.	For products currently subject to part 207, the electronic submission requirement in section 510(p) of the FD&C Act was largely implemented through FDA's 2009 electronic registration and listing guidance (74 FR 26248). Upon the effective date of this final rule, FDA expects continued electronic submission of registration and listing information in accordance with our electronic registration and listing guidance and with new § 207.61. This applies to newly submitted registration and listing information as well as updates to information previously submitted. FDA will accept waiver requests in accordance with § 207.65 of this final rule upon its effective date. Two years after the effective date of this final rule, FDA intends to remove from our current electronic database establishment registration and listing information submitted in the past on paper and not updated with a more recent electronic submission. The purpose of this removal is to purge outdated information from our database, such as information registrants failed to update after discontinuing a drug product or closing an establishment. Therefore, registrants must migrate their establishment registration and listing information to our electronic system (or obtain a waiver from the electronic submission requirement) before that time if they have not already done so. Registrants may not rely on a ''no changes'' certification to migrate information submitted in the past on paper to our electronic system. They must enter and transmit current registration and listing information to FDA electronically.
Electronic submission of blood establishment registration and listing information under amended part 607.	Owners or operators of human blood product establishments currently register and list either electronically or by submitting Form FDA 2830 by mail. FDA will stop accepting paper submissions and require electronic submission of establishment registration and product listing information under amended part 607, unless individual waivers are granted, 1 year after the effective date of this final rule.
Electronic submission of HCT/P establishment registration and listing information under part 1271.	Owners or operators of HCT/P establishments currently register and list either electronically or by submitting Form FDA 3356 by mail. FDA will stop accepting paper submissions and require electronic submission of establishment registration and product listing information under amended part 1271, unless individual waivers are granted, 1 year after the effective date of this final rule.
Part 207, Subpart B—Registration (timing of establishment registration and update submissions and substance of the information submitted).	Registrants are required to submit and update establishment registration information in accordance with amended subpart B of part 207 no later than the time when registration information is due after the first anniversary of the effective date of this final rule. If the effective date falls between October 1 and December 31, registrants must submit information required by amended subpart B no later than the next October through December annual review and update period. However, registrants must comply with new § 207.29(a) (expedited updates when certain establishment registration information changes) upon the effective date of this final rule.

TABLE 2—COMPLIANCE DEADLINES—Continued

Requirement	Effective date or compliance deadline
Part 207, Subpart D—Listing (timing of drug listing and update submissions and substance of the information submitted).	Registrants are required to submit and update drug listing information in accordance with amended subpart D of part 207 (including the submission of NDCs that are formatted in accordance with subpart C of part 207) no later than the time when listing information is due after the first anniversary of the effective date of this final rule. If the effective date falls during either June or December, registrants must submit information required by subpart D no later than the June or December listing update 12 months after the effective date.
Part 607—Establishment registration for blood and blood products	Registrants are required to submit and update establishment registration information in accordance with amended part 607 no later than the time when establishment registration information is due after the first anniversary of the effective date of this final rule. If the effective date falls between October 1 and December 31, registrants must submit establishment registration information required by amended part 607 no later than the next October through December annual review and update period. However, registrants must comply with new § 607.26 (amendments to establishment registration for certain changes such as ownership or location) upon the effective date of this final rule.
Part 607—Listing for blood and blood products	Registrants are required to submit and update product listing information in accordance with amended part 607 no later than the time when listing information is due after the first anniversary of the effective date of this final rule. If the effective date falls during either June or December, registrants must submit information required by subpart D no later than the June or December listing update 12 months after the effective date.
Part 1271—Establishment registration for HCT/Ps	Registrants are required to submit and update establishment registration information in accordance with amended part 1271 no later than the time when registration information is due after the first anniversary of the effective date of this final rule. If the effective date falls in December, registrants must submit establishment registration information required by amended part 1271 no later than the next December annual review and update period under § 1271.21(b).
Part 1271—Product listing for HCT/Ps	Registrants are required to submit and update listing information in accordance with amended part 1271 no later than the time when listing information is due after the first anniversary of the effective date of this final rule. If the effective date falls during either June or December, registrants must submit information required by amended part 1271 no later than the June or December listing update 12 months after the effective date.

V. Legal Authority

We have the legal authority to amend our regulations on foreign and domestic establishment registration and listing for human drugs, including drugs that are regulated under a BLA, and animal drugs. The statutory basis for our authority includes sections 201, 301, 501, 502, 503, 505, 506, 506A, 506B, 506C, 510, 512, 513–516, 518–520, 701, 704, 721, 801, and 903 of the FD&C Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 360, 360b, 360c–360f, 360h–360j, 371, 374, 379e, 381, and 393); 15 U.S.C. 1451–1561; sections 351 and 361 of the PHS Act (42 U.S.C. 262 and 264); and section 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

Section 510(c) of the FD&C Act requires every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug to immediately register with the Secretary his name, place of business, any such manufacturing establishments and their unique facility identifiers, and a point-of-contact email address. The provisions in section 510(b) and (d) of the FD&C Act require annual registration beginning on October 1 and ending on December 31 of each year and registration of additional establishments, respectively. Section 510(i) of the FD&C Act requires any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States to register with the Secretary by providing certain information. These provisions, together with section 701(a) of the FD&C Act (among others), authorize us to require the submission of the registration information specified in the final rule. The information specified in this final rule will help us identify who is manufacturing, repacking, relabeling, or salvaging drugs and where those operations are being performed. In addition, some information (*e.g.,* official contact information) will help us communicate with establishments more effectively and schedule inspections more efficiently.

Section 510(j)(1) of the FD&C Act requires every person who registers to file with the Secretary, at the time of registration, a list of all drugs that are being manufactured, prepared, propagated, compounded, or processed by the registrant for commercial distribution. That list must be prepared in the form and manner prescribed by the Secretary and must be accompanied by a copy of labeling (or the label and package insert) and, in some cases, advertising. Section 510(j)(2) of the FD&C Act requires listing information updates every June and December. This listing information gives us a current inventory of marketed drugs. These provisions of the FD&C Act and others, together with section 701(a) of the FD&C Act, provide authority for requiring the

submission of listing information set forth in this proposal. The drug listing information specified in this final rule will help us: (1) Develop a more current, robust inventory of drugs as a counter-terrorism measure; (2) more effectively administer our postmarketing surveillance programs; (3) facilitate recalls of products; (4) identify drugs or ingredients in short supply in the event of a national emergency; and (5) identify drugs marketed in violation of the law.

Section 510(b) of the FD&C Act requires that information registrants supply for annual registration includes a UFI for the establishment and includes a point-of-contact email address. FDA published final guidance in November 2014 specifying that FDA's preferred UFI for drug establishment registration is the DUNS number, assigned and managed by Dun & Bradstreet.

Section 510(p) of the FD&C Act requires electronic submission of establishment registration and listing information, unless FDA waives the electronic submission requirement in individual cases. Establishments that manufacture HCT/Ps currently register and list HCT/Ps under FDA's regulations in part 1271. Pursuant to authority under section 361 of the PHS Act, FDA is requiring electronic submission of registration and listing information for HCT/Ps.

Section 510(j) requires biannual updates of certain listing information. Requiring certification under section 701(a) authority will help us with the efficient enforcement of the FD&C Act because we will be able to distinguish between situations where there has been noncompliance with registration and listing requirements from situations where there have been no changes in information. The failure to register or list under section 510 is a prohibited act under section 301(p) of the FD&C Act, and the failure to do either renders a drug misbranded under section 502(*o*) of the FD&C Act.

VI. Analysis of Environmental Impact

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

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final requirements will not impose a significant burden on a substantial number of small entities (annualized costs represent at most, 0.01 percent of sales for small firms, and 0.002 percent for large firms, on average), we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Benefits and Costs

The full assessment of the economic analysis is available in Docket No. FDA–2005–N–0464 (Ref. 1) and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

The final rule clarifies and codifies the Congressionally mandated requirements in FDAAA and FDASIA, and adds a few additional requirements to the information needed to list products. The final rule will improve management of the establishment registration and drug listing requirements and make these processes more efficient and effective for industry and for FDA. Maintaining a comprehensive electronic registration and listing system supports implementation of the electronic prescribing provisions of the MMA. Because registrants submit electronic copies of the drug labeling with their drug listing, this rule also ensures the availability of current drug information through DailyMed, a computerized repository of drug labeling maintained by the National Library of Medicine. Establishment registration information helps FDA identify who is manufacturing, repacking, relabeling, and salvaging drugs and where those operations are performed. Quickly accessible electronic information about each establishment in the supply chain will help inform our enforcement efforts and improve our oversight of the entire drug supply chain. Product listing information also gives FDA a current inventory of drugs manufactured, repacked, relabeled, or salvaged for commercial distribution. Under current practices, registrants would only update listings when the listing information has changed. Consequently, some registrants have never submitted listings in an electronic format. By requiring electronic listings for all marketed drugs, the final rule will modernize our electronic systems and close an existing gap in data for drugs that are listed in our legacy system but not currently listed in our electronic system. Because the final rule primarily codifies current business practices, we anticipate that most of the benefits of a modern electronic drug registration and listing system were achieved as firms implemented electronic submissions in response to the FDAAA and FDASIA legislation. The incremental changes required by the final rule will yield benefits in addition to those already achieved. However, we lack sufficient information to quantify these marginal benefits.

Table 3 provides an itemized description of each incremental cost associated with registration and listing for part 207, part 607, and part 1271 registrants. For part 207 registrants, the final rule will require immediate source NDCs for unfinished drugs, listing missing inactive ingredients, and certification of no changes to their drug listings. Without the final rule, FDA faces an information gap because companies do not always notify the Agency when they stop marketing a product. For part 607 and part 1271 registrants, the requirements are quite slight for those that already submit registration and listing information electronically and minimal for the much smaller number of establishments that need to migrate their paper registration

and listing records to electronic format. All registrants will incur costs associated with reading and understanding the rule and revising their standard operating procedures (SOPs), and these items represent the largest incremental cost. Most incremental costs are one-time only; the only recurring costs are for part 207 registrants for certifying no changes to their listings the previous year when they renew their registrations.

TABLE 3—ITEMIZED INCREMENTAL COSTS

[$ millions] [1]

Incremental costs	Frequency	Number of hours per unit	Number of units	Total cost
Drugs and biological products (part 207):				
Identify source of unfinished drugs (from source NDCs).	Once	0.25	93,700 listings	$3.1
Listing inactive ingredients	Once	0.25	40,800 listings	1.4
Listing legacy products	Once	2.5	26,300 listings	8.7
Read and understand the final rule	Once	21	5,900 registrants	16.5
Revise SOPs for registration and listing	Once	19	5,900 registrants	14.9
Revise SOPs for reusing NDCs	Once	11	2,950 registrants	4.3
Certification of no-change	Recurring annually	0.5	7,300 establishments	0.5
Total costs (part 207)				49.4
Human-blood products (part 607):				
Read and understand the final rule	Once	14	2,700 registrants	5.0
Revise SOPs for registration and listing	Once	11	27 registrants	0.04
Migrating records to FDA's electronic systems	Once	1	27 registrants	0.0
Total costs (part 607)				5.1
Human-cell and tissue products (part 1271):				
Read and understand the final rule	Once	14	2,800 registrants	5.2
Revise SOPs for registration and listing	Once	11	280 registrants	0.4
Migrating records to FDA's electronic system	Once	1	280 registrants	0.0
Total costs (part 1271)				5.7

[1] We considered the length of the final rule, the number of small and large firms affected, and the extent each firm is affected in order to estimate the burden to read and understand the rule. For part 607 registration and listing, the cost estimate shown as $0.0 million represents $3,591. For part 1271 registration and listing, the cost estimate shown as $0.0 million represents $37,240.

Table 4 summarizes the total incremental costs; total annualized costs are $9.0 million when calculated at a 7-percent discount rate over 10 years, or $7.5 million when calculated using a 3-percent discount rate.

TABLE 4—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT

				Units			
Category	Primary estimate ($millions)	Low estimate ($millions)	High estimate ($millions)	Year dollars	Discount rate (percent)	Period covered (years)	Notes
Benefits:							
Annualized Monetized $ millions/year.					7 3		
Annualized Quantified					7 3		
Qualitative	The final rule will complete and codify modernization of the registration and listing system, thus allowing FDA to identify establishments, specific drugs or ingredients, to facilitate recalls or information alerts, and to exercise competent oversight of this important industry.						
Costs:							
Annualized Monetized $ millions/year.	$ 9.0 $ 7.5			2014 2014	7 3	10 10	Recurring costs include only annual time costs of certifying there are no changes to listings; these costs are unique to part 207 registrants.
Annualized Quantified					7 3		
Qualitative							
Transfers:							

TABLE 4—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT—Continued

				Units			
Category	Primary estimate ($millions)	Low estimate ($millions)	High estimate ($millions)	Year dollars	Discount rate (percent)	Period covered (years)	Notes
Federal Annualized Monetized $ millions/year.	.....	.....	.....	.....	7 3		
From/To	From:			To:			
Other Annualized Monetized $ millions/year.	.....	.....	.....	.....	7 3		
From/To	From:			To:			

Effects:

State, Local or Tribal Government: No estimated effect.

Small Business: The final rule will have little impact on small businesses; annualized costs represent, at most, 0.01 percent of annual sales for small firms and 0.002 percent for large firms, on average.

C. Response to Comments on the Preliminary Impact Analysis of the Proposed Rule

Most of the comments on the regulatory impact analysis of the proposed rule (PRIA) concerned the assignment of NDC numbers and the requirement that they be printed on container labels. Because these proposed changes are not included in the final rule, the comments are moot and are not discussed here. We also do not discuss the comments on the analysis of the proposed implementation of mandatory electronic registration and listing as this was mandated by FDAAA and largely implemented by guidance in 2009. Interested parties were able to comment on the burden estimates presented in the draft guidance entitled ''Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing'' when it was announced in the **Federal Register** of July 11, 2008 (73 FR 39964) (available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs). The remaining comments have been grouped by topic; the order in which they are discussed is not a reflection of importance.

(Comment 93) Some manufacturers believed the PRIA did not address the financial impact on their sector of the industry and disagreed with the Agency's assertion of no significant economic impact on a substantial number of small businesses. In particular, manufacturers of medical foods and medical devices did not believe we properly addressed the loss of revenue they could experience if they could not use NDC numbers on their products. Contract manufacturers felt there should be a separate analysis of their sector of the industry as did medical gas firms who asserted their numbers were underrepresented.

(Response) We disagree with the comments. NDC numbers were never intended for use on medical foods. The medical food industry began using NDCs to simplify reimbursement payments by insurance companies. There are other mechanisms that can be used for medical food product reimbursement, and the secondary impact from FDA enforcement of existing rules is not part of a regulatory impact analysis of new requirements. The Unique Device Identification System final rule (78 FR 58786, September 24, 2013) replaces the use of NDC numbers on medical devices with a UDI number. The impact of this change was accounted for in that rule.

The PRIA measured the incremental cost to comply with the new or changed requirements on a per-establishment and per-listing basis. Most of the data in the analysis of the proposed rule are not relevant for the final rule because mandatory electronic submission began in June 2009 with the statutory implementation authorized by FDAAA; however, the methodology is relevant. We estimated the incremental cost for registration on a per establishment basis. We included all registered establishments in our estimate, so establishments in all industry sectors required to register are included in the analysis if they comply with the requirement. The information required for each establishment is essentially the same. Any economies of scale for a large firm to register multiple establishments at one time are economically insignificant. The same is true for the incremental cost to list products. A contract manufacturer, or a repackager, may have more than one product to list, but the information required for each product is essentially the same for a contract manufacture and other manufacturers. The final rule provides that a private label distributer can list the products it distributes on behalf of contract manufacturers, but the legal obligation remains the contract manufacturers'.

The Regulatory Flexibility Act requires Agencies to assess the regulatory impact on domestic small entities and to analyze options that would lessen the burden on small entities. The Small Business Administration defines a drug manufacturer as small if it employs fewer than 750 people and a biological products entity as small if it employs fewer than 500.

The size of the entity is determined by the total employment of the ultimate parent firm, which can include companies outside the drug and biological products industries. For example, if a drug manufacturer's ultimate parent is a financial holding company that employs more than 750 people across a variety of industrial and service sectors, the firm would be considered large even if employment in drug manufacturing is only 100 employees.

For the proposed rule, we used a crude method, using U.S. Census information and a database of FDA's ''Approved Drug Products with Therapeutic Equivalence Evaluations'' (commonly referred to as the Orange Book) to characterize the number and size of the affected firms and used U.S.

Census data from the 2002 Economic Census and County Business Patterns for the financial information in the regulatory flexibility analysis. The Census data are reported by North American Industry Classification System codes (NAICS). Depending on the survey, the economic data are collected on an establishment or firm level. Companies whose primary NAICS code is not a drug or biologic manufacturer would not be included in the financial survey data. For example, the primary NAICS code for many small medical gas companies is not pharmaceutical preparations manufacturing (NAICS 325412), so these establishments are not included in the Census data for NAICS 325412. Including the financial data for medical gas establishments in the analysis would be optimal, but we are not aware of publicly available data that would capture this information. Although the financial information characterizing the industry did not include the medical gas sector, medical gas establishments were included in the burden estimates.

The regulatory impact analysis for this final rule uses Dun & Bradstreet information on total employment of the ultimate parent company to determine the size of entities affected by the rule, but we still use the Census data for NAICS 325412 and 325414 for the financial information because of limitations of available data.

There were a number of comments regarding the burden of submitting certain information in listing, in particular batch information, inactive ingredients, and certifying that there has been no change to a listing.

(Comment 94) Some comments noted that batch information is already included in annual reports for products that require applications, so the information is a duplication of effort. These comments also noted that this information can change often and adds an additional element that needs to be tracked and updated.

(Response) After considering the comments, FDA has decided not to include the batch information requirement in the final rule.

(Comment 95) Some comments suggested FDA reconsider the requirement or frequency of the requirement to certify that no change is necessary for listings every June and December. Using the 0.25-hour estimate from the proposed rule for the time required to verify and certify a listing, one company with 800 products calculated that it would take 114 hours (around 14, 8-hour days) twice a year to comply with the requirement, assuming about 60 percent of their total products did not require updates in June and December. Another company with over 7,000 products said it would take 6 months to validate and certify their listings with no changes. They suggested making the no changes certification requirement every 2 years rather than biannually. Another comment suggested that changing the requirement to certifying by establishment, rather than by listing, would result in a savings of $1 million per year.

(Response) After considering the comments, we have revised the requirement for no changes certification from a per-listing basis to an establishment basis. Rather than certifying each June and December that there is no change to each individual listing, registrants can certify by establishment that the electronically listed products are up to date when they annually renew their registrations.

(Comment 96) Some comments regarding submitting inactive ingredients as part of listing stated it was unnecessary, burdensome, and in some cases would result in the release of information a company considered proprietary. These comments noted that inactive ingredients are included in human and animal drug applications and must be listed on the labels of OTC products. Some manufacturers of animal drugs claimed that inactive ingredients are not customarily supplied on the label and were concerned with the release of proprietary information.

(Response) Although inactive ingredients are identified in product applications and, in many cases, on product labels, the information is not easily accessible and the names are not fully standardized. Listing is the only mechanism by which FDA can readily access ingredient information across all products. Entering the inactive ingredients using defined terminology increases the accuracy and the efficiency of data searches. We use the information in listing to inform many processes FDA uses for protecting public health, including surveillance for serious drug adverse reactions, inspection of facilities used for drug manufacturing and processing, and monitoring drug products imported into the United States. To prevent public disclosure of information a registrant views as confidential, an inactive ingredient can be designated as confidential during the listing process.

VIII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

Description: The final rule reorganizes, consolidates, clarifies, and modifies current regulations on registering establishments and listing drugs codified in part 207 for human and animal drugs, in part 607 for blood and blood products, and in part 1271 for HCT/Ps. The final rule describes when and how to register and list and what information must be submitted for registration and listing. The final rule clarifies the NDC system for drugs and requires that each drug product subject to the listing requirements of this final rule have a unique NDC.

The final rule codifies the current statutory requirement that registration and listing information be submitted to FDA electronically instead of using paper forms unless a waiver is obtained. Historically, drug establishment registration and drug listing information was submitted using Form FDA 2656 (Registration of Drug Establishment/Labeler Code Assignment), Form FDA 2657 (Drug Product Listing), and Form FDA 2658 (Registered Establishments' Report of Private Label Distributors). Before the enactment of FDAAA, section 510(p) of the FD&C Act expressly provided for electronic submission of drug establishment registration information upon a finding that electronic receipt was feasible, and section 510(j) of the FD&C Act specified that drug listing information was to be prepared in the form and manner prescribed by FDA. Section 224 of FDAAA, which amended section 510(p) of the FD&C Act, now requires electronic drug listing in addition to electronic drug establishment registration. In certain cases, and as discussed in section VIII.E, if it is unreasonable to expect a person to submit registration and listing information electronically, FDA may grant a waiver from the electronic submission requirement.

In June 2009, FDA made available the electronic registration and listing

guidance (74 FR 26248, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) to provide recommendations on fulfilling the statutory requirement to submit electronically drug establishment registration and drug listing information. The guidance describes the types of information to include for purposes of drug establishment registration and drug listing and how to prepare and submit the information in an electronic format (Structured Product Labeling (SPL) files) that FDA can process, review, and archive. In June 2009, FDA began accepting submissions required under the part 207 regulations into our electronic drug registration and listing system. The format for these electronic submissions employs Extensible Markup Language (XML) and uses the SPL standard to organize the data within the file. This electronic registration and listing enables FDA to employ a number of automated validations to ensure the quality of the data received.

In addition to the information that previously was collected on the FDA forms, the electronic registration and listing guidance addresses, with respect to part 207, the electronic submission of other statutorily required information as follows:

- The name of each importer that is known to the establishment (the U.S. 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) (section 510(i)(1)(A) of the FD&C Act);
- The name of each person who imports or offers the foreign establishment's drug for import (the name of each agent, broker, or other entity, other than a carrier, that the foreign drug establishment uses to facilitate the import of its drug into the United States) (section 510(i)(1)(A) of the FD&C Act); and
- For a registered foreign drug establishment, the name, address, and telephone number of its U.S. agent (§ 207.40(c)).

The electronic registration and listing guidance also recommends the voluntary submission of the following additional information, when applicable:

- The email address for the United States agent, and the telephone number(s) and email address for the importer and person who imports or offers for import their drug;
- A site-specific Data Universal Numbering System (DUNS) number for each entity (in November 2014, we issued the guidance for industry entitled ''Specification of the Unique Facility Identifier System for Drug Establishment Registration'' (79 FR 65977, available on the Internet at *http://www.fda.gov/Drugs* under Guidances (Drugs)) and obtained OMB approval to broaden the entity identification number covered in OMB control number 0910–0045);
- The NDC product code for the source drug that is repacked or relabeled;
- Distinctive characteristics of certain listed drugs (*i.e.,* the flavor, the color, and image of the actual solid dosage form); and
- Registrants may indicate that they view as confidential an inactive ingredient or the registrant's business relationship with an establishment.

We currently have OMB approval under the PRA (OMB control number 0910–0045) for the information collection in current part 207, the information that was submitted using Form FDA 2656, Form FDA 2657, and Form FDA 2658, and the information collection set forth in the electronic registration and listing guidance, including the electronic submission of registration and listing information as required by FDAAA. The information collection for current part 607 is approved by OMB under OMB control number 0910–0052. The information collection for current part 1271 is approved by OMB under OMB control number 0910–0543.

In tables 5, 6, 7, and 8, we estimate the total burden to comply with the applicable information collection requirements for parts 207, 607, and 1271 as set forth in this final rule. These burden estimates for the applicable regulations will replace some of the currently approved estimates in OMB control numbers 0910–0045, 0910–0052, and 0910–0543. These estimates are based on FDA's experience with reviewing registration and listing submissions under part 207 since June 2009 and on the number of submissions currently received, the number of respondents submitting this information, and the number of registered establishments and listed drugs, blood products, and HCT/Ps currently in FDA's drug registration and listing database.

A. Registration Information Collection Under Part 207

1. Requirements

Under § 207.17, manufacturers, repackers, relabelers, and drug product salvagers must register their establishments. This is consistent with current registration information collection, except that PET drug producers are not exempt from registration under the final rule, and the final rule states that FDA will accept registration information from a private label distributor if it is acting as an authorized agent for and submitting information that pertains to an establishment that manufactures, repacks, relabels, or salvages drugs.

Under § 207.21, domestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers must complete initial registration of each establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug. In addition, foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers must register each establishment before the drug is imported or offered for import into the United States. This is consistent with current registration information collection.

The information that must be provided to FDA for registration is described in § 207.25. The final rule does not require the following currently required information collection:

- Kind of ownership or operation.
- Title of each corporate officer and director.

The final rule requires the following new registration information collection:

- Type of operations performed at each establishment.
- Contact information for the establishment's official contact.

Under § 207.29, registrants must review their registration information annually between October 1 and December 31and report all changes to their registration information or certify that no changes have occurred. In addition to the annual review and update, registrants must submit expedited reports of certain changes within 30 calendar days of the change. Currently, registrants must renew their registration information annually and submit certain amendments to registration within 5 days of a change. Section 207.29 differs from the current requirement to submit amendments to registration in the following ways:

- The final rule lengthens the current time period for reporting changes to registration information from 5 days (10 business days for a change in United States agent information) to 30 calendar days.
- The final rule revokes the current requirement to report a change in individual ownership and corporate or partnership structure and the current requirement to submit a signed

statement for a change in a registered establishment's firm name.

New registration information collected under the final rule includes the certification that no changes have occurred and reporting certain changes as expedited updates within 30 calendar days.

2. Burden Estimates

Based on the number of new establishments that currently register each year, we estimate that approximately 1,400 registrants will submit electronically approximately 2,800 new establishment registrations annually. Based on the number of registered establishments in our database, we estimate that approximately 10,000 registrants will provide approximately 10,000 annual reviews and updates of registration information (including expedited updates) or reviews and certifications that no changes have occurred.

The estimates include the registration of establishments for both domestic and foreign manufacturers, repackers, relabelers, and drug product salvagers, and registration information submitted by anyone acting as an authorized agent for an establishment that manufactures, repacks, relabels, or salvages drugs. The estimates include an additional 80 PET drug producers who are not exempt from registration under the final rule and approximately 30 manufacturers of plasma derivatives.

We estimate that it will take approximately 1 hour for registrants to submit initial registration information electronically for each new establishment.

We also estimate that it will take approximately 30 minutes for each annual review and update of registration information (including any expedited updates) or each review and certification that no changes have occurred.

The burden hour estimates are based on our familiarity with the amount of time it takes registrants to input registration information electronically since June 2009. The estimates are an average of the time it would take to register a domestic or foreign establishment and an average of the time it would take to review registration information and update several registration items in the database or review registration information and only certify that no changes have occurred.

B. Listing Information Collection Under Part 207

1. Requirements

Under § 207.41, registrants must list drugs they manufacture, repack, relabel, or salvage for commercial distribution. This requirement is consistent with current listing information collection, except that drug product salvagers are not currently required to list under part 207.

The final rule revises current NDC-related listing submissions as follows:

- A registrant must list each drug it manufactures, repacks, or relabels using an NDC that includes the registrant's own labeler code, regardless of whether the drug is commercially distributed under the registrant's own label or trade name or under the label or trade name of a private label distributor.
- Each registrant must list each drug it manufactures, repacks, or relabels for commercial distribution under the trade name or label of a private label distributor using an NDC that includes such private label distributor's labeler code.
- During listing, each manufacturer, repacker, or relabeler must propose for assignment by FDA an NDC that includes its own labeler code for each package size and type of drug that it manufactures, repacks, or relabels for commercial distribution.
- If a drug is distributed under the trade name or label of a private label distributor, the manufacturer, repacker, or relabeler must also propose for assignment by FDA an NDC that includes the labeler code of the private label distributor under whose trade name or label the drug is distributed, for each package size and type so distributed.
- A manufacturer, repacker, relabeler, or private label distributor may also reserve a proposed NDC for a drug, before the drug is listed, by submitting certain information.

Under § 207.45, registrants must list, no later than 3 calendar days after the initial registration of each establishment, any drug being manufactured, repacked, relabeled, or salvaged for commercial distribution at that establishment. This requirement is consistent with current listing information collection, except that the final rule specifies within 3 calendar days after initial registration.

Under the final rule, the information registrants must submit to list a drug, including the information that must be submitted (by a registrant or a private label distributor) to receive a labeler code, is described in §§ 207.33, 207.49, 207.53, 207.54, 207.55, and 207.61. Under current part 207, we assign a labeler code to each registrant and the registrant assigns the product code and the package code for each drug product's NDC.

The listing and NDC information collections required by the final rule are already approved by OMB under OMB control number 0910–0045, except for the following: (1) The name of each inactive ingredient in a listed drug (assertions of confidentiality associated with individual inactive ingredients are covered in the electronic registration and listing guidance); (2) additional information, such as email address, to identify a domestic registrant (identifying information for foreign registrants is part of the electronic registration and listing guidance information collection and in current § 207.40(c)); (3) the drug master file or veterinary master file number, if one exists, must be submitted by the manufacturer for an unfinished drug; (4) drug product salvagers (who do not repack or relabel) must submit the lot number and expiration date and NDC assigned to the drug immediately before the drug is received by the drug product salvager; (5) all new labeling for a repacked or relabeled drug must be submitted, and not only the changed labeling; (6) package type and volume information corresponding to the package code segment of the NDC must be submitted; (7) a drug's OTC monograph reference (if any) and the date on which the drug was or will be introduced into commercial distribution are both requested for voluntary submission; and (8) the name and Unique Facility Identifier (UFI) of the establishment where the registrant who lists the drug manufactures it and the type of operation performed on the drug at that establishment, and, if an immediate source NDC is not provided, the name and UFI of every other establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment must be provided.

Under § 207.57, registrants must update drug listing information submitted previously (either when the change is made or, at a minimum, each June and December). Registrants must also notify FDA if any listed drug has been discontinued from marketing or if any discontinued drug has been reintroduced and provide listing information for any drug not yet listed (at the time of annual establishment registration if not sooner). Under § 207.35, registrants must notify us of a change in any of the drug characteristics (except certain identifying information) for an NDC in § 207.33, and assign a new product code and package code for that drug. Current listing information collection does not specifically require any type of certification if there are no

changes, and only material changes to listing information must be reported.

2. Burden Estimates

Based on the number of drugs listed annually since June 2009, we estimate that approximately 1,713 registrants will submit electronically approximately 12,469 new listings annually (including the information submitted to obtain a labeler code and to reserve an NDC for future use).

Based on the number of drugs in our listing database and the current number of changes to listing information submitted, we estimate that approximately 5,300 registrants will provide approximately 10,000 June and 10,000 December reviews and updates of listing information—a total of approximately 20,000 submissions annually (including the information submitted to revise an NDC).

The estimates for the number of drug listings include both domestic and foreign listings, listings submitted by registrants for products sold under their own names as well as products intended for private label distribution, and information submitted related to an NDC and to obtain a labeler code. The estimate for the number of drugs subject to the listing requirements includes PET drugs and approximately 30 plasma derivatives. The estimates for the number of June and December reviews and updates of listing information include the number of changes to drug characteristics pertaining to the drug product code to obtain a new NDC and the reports of the withdrawal of an approved drug from sale under § 314.81(b)(3)(iii).

Based on our familiarity with the time required to input listing information electronically since June 2009, we estimate that it will take registrants approximately 1 hour and 30 minutes to submit information electronically for each drug they list for the first time (for both foreign and domestic registrant listings). These estimates are an average of the time it will take manufacturers, repackers, relabelers, and drug product salvagers, with drug product salvagers taking considerably less time than manufacturers. The estimates include the time for submitting the content of labeling and other labeling in electronic format. (For drugs subject to an approved marketing application, the electronic submission of the content of labeling under current § 314.50(l)(1)(i) is also approved under OMB control number 0910–0001.) We also estimate that it will take approximately 45 minutes for each June and December review and update of listing information. These estimates are an average of the time it would take to review and update listing information or to review and certify that no changes have occurred. The estimates include the time for submitting any labeling for each drug, changes to the drug's characteristics submitted for a new NDC, and reports of the withdrawal of an approved drug from sale under § 314.81(b)(3)(iii).

C. Registration and Listing Information Collection Under Part 607

1. Requirements

Under § 607.22(a) of the final rule, blood establishments must submit initial and subsequent registration and product listing electronically through the Blood Establishment Registration and Product Listing system, or any future superseding electronic system. All information submitted under this part must be transmitted to FDA electronically. Currently, under § 607.22, manufacturers must register establishments and list blood products on Form FDA 2830. The requested information is consistent with the current requirement to register establishments and list products approved under OMB control number 0910–0052. A separate discussion regarding waivers under § 607.22(b) is discussed in section E.

Under §§ 607.25(a) and 607.25 (b)(3) of the final rule, establishments must include the Unique Facility Identifier as part of the registration and product listing. The other requested information under this regulation is consistent with the current requirements to register establishments and list products approved under OMB control number 0910–0052.

Under § 607.25(b)(1) of the final rule, blood establishments are required to list blood products by the established and proprietary name. This is consistent with the current listing requirement approved under OMB control number 0910–0052. Currently, manufacturers of plasma derivatives and bulk product substances register and list under both parts 607 and 207. The final rule revises this requirement by requiring persons who engage solely in the production of plasma derivatives, bulk product substances, and recombinant version of plasma derivatives or animal derived plasma derivatives to register and list only under part 207. Any reduction in burden is expected to be minimal (approximately 20 establishments) and will be reflected under OMB control number 0910–0052. To be consistent with part 207, we are also deleting the reference in part 607 to Form FDA 2250 (National Drug Code Directory Input) because this form is no longer being used by CDER or CBER.

Under current § 607.40, foreign establishments must include information for the United States agent as part of its initial and updated registration. The final rule requires submission of minimal additional information (*i.e.,* email address) for the United States agent. This information is consistent with the current registration information approved under OMB control number 0910–0052. The final rule requires the foreign establishment to report to FDA changes in the United States agent's name, address, telephone number, and email address within 30 calendar days of the change. The final rule lengthens from 10 business days to 30 calendar days the time period for reporting changes in the United States agent's information to FDA.

2. Burden Estimates

Based on the number of new establishments that currently register with FDA each year, we estimate 68 establishments will provide new establishment registration and product listings annually under §§ 607.22(a), 607.25(a), and (b)(3).

We estimate that it takes approximately 60 minutes to provide the initial registration and listing information for each new establishment.

Based on the number of establishments that currently submit registration and product listing updates, we estimate 2,615 establishments will provide establishment registration and product listing updates annually under §§ 607.22(a), 607.25(a), and (b)(3).

We estimate that it takes approximately 30 minutes to provide the establishment registration and listing update information for establishment.

These burden hour estimates are based on institutional experience with the current registration and listing requirements.

D. Registration and Listing Information Collection Under Part 1271

1. Requirements

Under § 1271.22, establishments must register, list products, and provide updates electronically. The current regulation includes the option to submit registration, listing, and updates electronically.

Under § 1271.25, establishments must also submit the telephone number and email address of the reporting official. Each foreign establishment must submit the name, the address, telephone number, and email address of each importer that is known to the

establishment and the name of each person who imports or offers for import such HCT/P to the United States. Foreign establishments must also submit the name, the address, telephone number, and email address of their United States agent.

Under § 1271.26, establishments must report a change to the United States agent's name, address, telephone number, or email address. The final rule will also lengthen to 30 calendar days the current requirement of reporting the changes within 5 days.

2. Burden Estimates

Based on the number of new establishments that currently register with FDA each year, we estimate that approximately 225 establishments will provide new establishment registration annually. Based on information from FDA's database, we estimate that approximately 2,700 establishments are registered and listed with FDA and will provide establishment and listing updates. The number of establishments that currently register and list with FDA includes both foreign and domestic establishments. If no change has occurred, an update is not required. Based on the number of establishments from FDA's database, we estimate that approximately 1,200 establishments will provide changes to establishment ownership or location, or changes to the United States agent's information.

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

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

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

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

E. Waiver Request Information

1. Part 207

Under § 207.65, registrants may request a waiver from the requirement in § 207.61 that information must be provided to us in electronic format. We expect very few waiver requests because only a computer, Internet access, and an email address are needed to register and list electronically and because electronic submission has been required since June 2009.

We estimate that approximately one registrant will request a waiver annually and that each request will take approximately 30 minutes to prepare and submit to us.

2. Part 607

Under § 607.22(b), both domestic and foreign establishments may request a waiver from the requirement that information must be provided to FDA in electronic format. We expect few waiver requests because only a computer, Internet access, and an email address are needed to register and list electronically.

We estimate that approximately 25 manufacturers will request a waiver annually and that each request will take approximately 1 hour to prepare and submit to us.

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

3. Part 1271

Under § 1271.23, manufacturers may request a waiver from the requirement in § 1271.22 that information must be provided to FDA in electronic format. We expect a limited number of waiver requests because only a computer, Internet access, and an email address are needed to register and list electronically.

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

When we grant a request for a waiver, we intend to make available to the manufacturer the paper form—revised Form FDA 3356 for registration and listing.

F. Public Disclosure Exemption Requests

Under § 207.81(c), registrants may request that certain information in § 207.81(a) not be made available from their registration and listing information. Based on our experience with registration and listing information inspection requests under current § 207.37, we estimate that approximately 100 registrants will submit this request annually and that each request will take approximately 1 hour to prepare and submit to us. (Assertions of confidentiality associated with individual inactive ingredients or the registrant's business relationship with an establishment is part of the June 2009 electronic registration and listing guidance information collection and is covered under OMB control number 0910–0045).

G. Standard Operating Procedure for Electronic Submission

The requirement under section 510(p) of the FD&C Act for electronic drug establishment registration and electronic drug listing resulted in our amending OMB control number 0910–0045 in June 2009 to include the burden for preparing a standard operating procedure (SOP) for the electronic submission requirement, creating the SPL file, including accessing and reviewing the technical specifications and instructional documents provided by FDA, reviewing and selecting appropriate terms and codes used to create the SPL file, obtaining the digital certificate used with FDA's electronic submission gateway, and uploading the SPL file for submission. Although most registrants have already prepared an SOP for the electronic submission requirements, each year additional firms will need to create an SOP. As provided in table 6, FDA estimates that approximately 1,000 firms will have to expend a one-time burden to prepare, review, and approve an SOP, and we estimate that it will take approximately 40 hours per recordkeeper to create 1,000 new SOPs, for a total of 40,000 hours. We also estimate approximately 3,295 hours for annual recordkeeping maintenance of these records.

H. Capital Costs

There are one-time capital costs associated with this rulemaking. These costs are discussed in section VII, ''Economic Analysis of Impacts.''

Description of Respondents: Manufacturers, repackers, relabelers, drug product salvagers, and private label distributors as described in the final rule.

Burden Estimate: Tables 5, 6, 7, and 8 provide the annual reporting and recordkeeping burdens for this final rule.

TABLE 5—ESTIMATED ANNUAL REPORTING BURDEN UNDER PART 207

21 CFR Sections and reporting requirements	Number of respondents	Number of responses per respondent	Total annual responses	Hours per registration or listing	Total hours
Initial Establishment Registration (§§ 207.17, 207.21, 207.25)	1,400	2	2,800	1	2,800
Annual Review and Update of Registration Information (including expedited updates) (§ 207.29)	10,000	1	10,000	0.50	5,000
Initial Listing (including NDC) Information (§§ 207.33, 207.41, 207.45, 207.49, 207.53, 207.54, 207.55)	1,713	7.28	12,470	1.5	18,705
June and December Review and Update (or Certification) of Listing (including NDC) Information (§§ 207.35, 207.57)	5,300	20	106,000	0.75	79,500
Waiver requests (§ 207.65)	1	1	1	0.50	0.5
Public disclosure exemption requests (§ 207.81(c))	100	1	100	1	100
Total Reporting Burden					106,105

TABLE 6—ESTIMATED ANNUAL RECORDKEEPING BURDEN UNDER PART 207

SOP for creating and uploading the SPL File	Number of recordkeepers	Number of records per Recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
One-time preparation of SOP	1,000	1	1,000	40	40,000
SOP maintenance	3,295	1	3,295	1	3,295
Total					43,295

TABLE 7—ESTIMATED ANNUAL REPORTING BURDEN UNDER PART 607

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Initial Establishment Registration and Product Listing (607.22(a) and 607.25(a) and (b)(3))	68	1	68	1	68
Annual Review and Update of Establishment Registration and Blood Product Listing (607.22(a) and 607.25(a) and (b)(3))	2,615	1	2,615	0.5	1,308
Waiver requests (607.22(b))	25	1	25	1	25
Total Reporting Burden					1,401

TABLE 8—ESTIMATED ANNUAL REPORTING BURDEN UNDER PART 1271

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Initial Establishment Registration and Listing (1271.25)	225	1	225	0.75	168.75
Annual Review and Update of Establishment Registration and Listing (1271.25)	2,700	1	2,700	0.5	1,350
Waiver requests (1271.23)	100	1	100	1	100
Amend Establishment Registration (1271.26)	1,200	1	1,200	0.25	300
Total Reporting Burden					1,918.75

The information collection provisions of this final rule have been submitted to OMB for review, as required by section 3507(d) of the PRA. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

X. References

The following reference is on display in the Division of Dockets Management, (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday. It is also available electronically at *http://www.regulations.gov and at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

1. FDA/Economics Staff, ''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, Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis,'' 2016.

List of Subjects

21 CFR Part 20

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

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 207

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 314

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

21 CFR Parts 514 and 515

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

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 607

Blood.

21 CFR Part 1271

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

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

PART 20—PUBLIC INFORMATION

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

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

§ 20.100 [Amended]

■ 2. Amend § 20.100(c)(9) by removing ''§ 207.37'' and by adding in its place ''§ 207.81''.

■ 3. Revise § 20.116 to read as follows:

§ 20.116 Drug and device registration and listing information.

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

PART 201—LABELING

■ 4. The authority citation for part 201 continues to read as follows:

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

§ 201.1 [Amended]

■ 5. Amend § 201.1(f) by removing ''§ 207.3(b)'' and adding in its place ''§ 207.1''.

§ 201.2 [Amended]

■ 6. Amend § 201.2 by removing the last sentence.

■ 7. In § 201.25 revise the first sentence of paragraph (c)(1) introductory text to read as follows:

§ 201.25 Bar code label requirements.

* * * * *

(c) * * *

(1) Each drug product described in paragraph (b) of this section must have a bar code that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code that meets European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standards or another standard or format that has been approved by the relevant Food and Drug Administration Center Director. * * *

* * * * *

■ 8. Revise part 207 to read as follows:

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

Subpart A—General

Subpart B—Registration

Subpart C—National Drug Code

Subpart D—Listing

Subpart E—Electronic Format for Registration and Listing

Subpart F—Miscellaneous

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

Subpart A—General

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

The definitions and interpretations of terms in sections 201 and 510 of the Federal Food, Drug, and Cosmetic Act apply to the terms used in this part, if not otherwise defined in this section. The following definitions apply to this part:

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

Bulk drug substance, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, means the same as ''active pharmaceutical ingredient'' as defined in § 207.1(b).

Commercial distribution means any distribution of a human drug, except for investigational use under part 312 of this chapter, and any distribution of an animal drug or an animal feed bearing or containing an animal drug, except for investigational use under part 511 of this chapter. The term does not include internal or interplant transfer between registered establishments under common ownership and control, including a parent, subsidiary, or affiliate company. For foreign establishments that manufacture, repack, relabel, or salvage, or for foreign private label distributors, the term ''commercial distribution'' has the same meaning except the term does not include distribution of any drug that is neither imported nor offered for import into the United States.

Content of labeling means:

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

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

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

(4) For animal drugs (including, but not limited to, drugs that are subject to section 512 of the Federal Food, Drug, and Cosmetic Act): The content of the labeling that accompanies the drug that is necessary to enable safe and proper administration of the drug (*e.g.,* the labeling applicable to veterinary drugs specified in part 201 of this chapter), including all text, tables, and figures.

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

Drug, for the purposes of registration and listing under this part, has the meaning given in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act.

Establishment means a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for a registered drug establishment (*e.g.,* consulting laboratories), manufacturers of medicated feeds and of vitamin products that are drugs in accordance with section 201(g) of the Federal Food, Drug, and Cosmetic Act, human blood donor centers, and animal facilities used for the production or control testing of licensed biologicals, and establishments engaged in salvaging.

Establishment registration number means the number assigned to the establishment, as identified by FDA, after the establishment registration required in this part.

Finished drug product means a finished dosage form (*e.g.,* tablet, capsule, or solution) that contains at least one active pharmaceutical ingredient, generally, but not necessarily, in association with other ingredients in finished package form suitable for distribution to pharmacies, hospitals, or other sellers or dispensers of the drug product to patients or consumers.

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

(1) When used to modify the term ''manufacturer,'' ''repacker,'' ''relabeler,'' or ''salvager,'' refers to a manufacturer, repacker, relabeler, or salvager, who is located in a foreign country and who manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States.

(2) When used to modify the term ''establishment'' refers to an establishment that is located in a foreign country and is engaged in the manufacture, repackaging, relabeling, or salvaging of any drug, or any animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States.

Importer means, for purposes of this part, a person in the United States that is an owner, consignee, or recipient, at the time of entry, of a foreign establishment's drug, or an animal feed bearing or containing a new animal drug, that is imported into the United States.

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

Manufacturer means a person who owns or operates an establishment that manufactures a drug or an animal feed bearing or containing a new animal drug. This term includes, but is not limited to, control laboratories, contract laboratories, contract manufacturers, contract packers, contract labelers, and other entities that manufacture a drug, or an animal feed bearing or containing a new animal drug, as defined in this paragraph. For purposes of this part,

and in order to clarify the responsibilities of the entities engaged in different operations, the term manufacturer is defined and used separately from the terms relabeler, repacker, and salvager, although the term ''manufacture, preparation, propagation, compounding, or processing,'' as used in section 510 of the Federal Food, Drug, and Cosmetic Act, includes the activities of relabelers, repackers, and salvagers. Repackers, relabelers, and salvagers are subject to the provisions of this part that are applicable to repackers, relabelers, and salvagers, but are not subject to the provisions of this part that are applicable to manufacturers. When not modified by ''domestic'' or ''foreign,'' the term includes both domestic manufacturers and foreign manufacturers.

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

Outsourcing facility means a compounder that has elected to register with FDA under section 503B of the Federal Food, Drug, and Cosmetic Act and that meets all of the conditions of section 503B.

Person who imports or offers for import means, for purposes of this part, the owner or exporter of a drug who consigns and ships a drug from a foreign country to the United States. This includes persons who send a drug to the United States by international mail or other private delivery service, but it does not include carriers who merely transport the drug.

Private label distribution means commercial distribution of a drug under the label or trade name of a person who did not manufacture, repack, relabel, or salvage that drug.

Private label distributor means, with respect to a particular drug, a person who did not manufacture, repack, relabel, or salvage the drug but under whose label or trade name the drug is commercially distributed.

Registrant means any person that owns or operates an establishment that manufactures, repacks, relabels, or salvages a drug, and is not otherwise exempt from establishment registration requirements under section 510 of the Federal Food, Drug, and Cosmetic Act or this part.

Relabel means to change the existing label or labels on a drug or drug package, or change or alter the existing labeling for a drug or drug package, without repacking the drug or drug package. This term does not include the addition or modification of information affixed solely for purposes of delivery to a customer, customer identification, and/or inventory management.

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

Repack or repackage means the act of taking a finished drug product or unfinished drug from the container in which it was placed in commercial distribution and placing it into a different container without manipulating, changing, or affecting the composition or formulation of the drug.

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

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

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

Salvage means the act of segregating out those finished 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 and includes applying manufacturing controls such as those required by current good manufacturing practice in parts 210 and 211 of this chapter.

Salvager means a person who owns or operates an establishment that engages in salvaging. When not modified by ''domestic'' or ''foreign,'' the term includes both domestic and foreign salvagers.

Unfinished drug means an active pharmaceutical ingredient either alone or together with one or more other ingredients but does not include finished drug products.

§ 207.3 Bulk drug substance.

Bulk drug substance, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as ''active pharmaceutical ingredient'' as defined in § 207.1(b).

§ 207.5 What is the purpose of this part?

Establishment registration information helps FDA identify who is manufacturing, repacking, relabeling, and salvaging drugs and where those operations are performed. Drug listing information gives FDA a current inventory of drugs manufactured, repacked, relabeled, or salvaged for commercial distribution. Both types of information facilitate implementation and enforcement of the Federal Food, Drug, and Cosmetic Act and are used for many important public health purposes.

§ 207.9 Who does this part cover?

(a) Except as provided in paragraph (b) of this section, this part applies to:

(1) Domestic manufacturers, domestic repackers, domestic relabelers and domestic salvagers, not exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act or § 207.13, regardless of whether their drugs enter interstate commerce;

(2) Foreign manufacturers, foreign repackers, foreign relabelers and foreign salvagers, not exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act or § 207.13;

(3) Private label distributors, because they must have labeler codes;

(4) Establishments engaged in the manufacture, repacking, relabeling, or salvaging of human drugs regulated under a biologics license application (BLA). These establishments are subject to the requirements of this part unless they are required to register and list such drugs as human blood or blood products under part 607 of this chapter and do not engage in activities that would otherwise require them to register and list under this part.

(5) Establishments engaged in the manufacture (as defined in § 1271.3(e) of this chapter) of human cells, tissues, and cellular and tissue-based products (HCT/Ps) (as defined in § 1271.3(d) of this chapter) that, under § 1271.20 of this chapter, are also drugs regulated under section 351 of the Public Health Service Act or section 505 of the Federal Food, Drug, and Cosmetic Act. These establishments must register and list those HCT/Ps following the procedures described in this part.

(b) This part does not apply to owners and operators of establishments that collect or process human whole blood

and blood products unless the establishment also manufactures, repacks, or relabels other drugs. For purposes of this paragraph (b), human whole blood and blood products do not include plasma derivatives such as albumin, Immune Globulin, Factor VIII and Factor IX, and recombinant versions of plasma derivatives or animal derived plasma derivatives, or bulk product substances such as fractionation intermediates or pastes. Establishments that collect or process human whole blood and blood products as well as establishments involved in testing of human whole blood and blood products must register and list under part 607 of this chapter. Manufacturers of licensed devices and manufacturers of licensed biological products used in a licensed device must register and list under part 607 of this chapter.

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

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

Except as provided in § 207.13(l), the following classes of persons are exempt from registration and drug listing in accordance with section 510(g) of the Federal Food, Drug, and Cosmetic Act or because FDA has determined, under section 510(g)(5) of the Federal Food, Drug, and Cosmetic Act, that their registration is not necessary for the protection of the public health. This exemption is limited to establishment registration and drug listing requirements and does not relieve a person from other statutory or regulatory obligations.

(a)(1) Pharmacies that:

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

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

(iii) Do not manufacture, repack, relabel, or salvage drugs other than in the regular course of their business of dispensing or selling drugs at retail.

(2) The exemption in this paragraph (a) is limited to pharmacies located in any State as defined in section 201(a)(1) of the Federal Food, Drug, and Cosmetic Act.

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

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

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

(iii) Do not manufacture, repack, relabel, or salvage drugs other than in the regular course of their practice of pharmacy, including dispensing.

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

(c) Individuals or establishments under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment to become components of a biological product are exempt from registration and listing under this part unless FDA determines that drug establishment registration and listing is necessary for the protection of the public health.

(d) 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.

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

(f) Manufacturers, repackers, and relabelers of harmless inactive ingredients such as excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs.

(g) Manufacturers, repackers, relabelers, or salvagers of Type B or Type C medicated feeds, except for persons who manufacture, repack, relabel, or salvage Type B or Type C medicated feeds starting from Category II, Type A medicated articles for which a medicated feed mill license approved under part 515 of this chapter is required. This exemption also does not apply to persons that would otherwise be required to register (such as manufacturers, repackers, relabelers, or salvagers of certain free-choice feeds, as defined in § 510.455 of this chapter, or certain liquid feeds, as defined in § 558.5 of this chapter, where the specifications and/or formulas are not published and a medicated feed mill license is required). All manufacturers, repackers, relabelers, or salvagers of Type B or Type C medicated feeds are exempt from listing.

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

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

(j) Foreign establishments whose drugs are imported or offered for import into the United States must comply with the establishment registration and listing requirements of this part unless exempt under this section or unless:

(1) Their drugs enter a foreign trade zone and are re-exported without having entered U.S. commerce, or

(2) Their drugs are imported in conformance with section 801(d)(3) of the Federal Food, Drug, and Cosmetic Act.

(k) Entities that are registered with FDA as outsourcing facilities and that compound drugs in conformance with section 503B of the Federal Food, Drug, and Cosmetic Act.

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

(1) Manufacture (as defined in § 207.1(b)), repack, relabel, or salvage compounded positron emission tomography drugs as defined in section 201(ii) of the Federal Food, Drug, and Cosmetic Act;

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

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

Subpart B—Registration

§ 207.17 Who must register?

(a) Unless exempt under section 510(g) of the Federal Food, Drug, and Cosmetic Act or this part, all

manufacturers, repackers, relabelers, and salvagers must register each domestic establishment that manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, and each foreign establishment that manufactures, repacks, relabels, or salvages a drug, or an animal feed bearing or containing a new animal drug, that is imported or offered for import into the United States. When operations are conducted at more than one establishment and common ownership and control among all the establishments exists, the parent, subsidiary, or affiliate company may submit registration information for all establishments.

(b) Private label distributors who do not also manufacture, repack, relabel, or salvage drugs are not required to register under this part. FDA will accept registration or listing information submitted by a private label distributor only if it is acting as an authorized agent for and submitting information that pertains to an establishment that manufactures, repacks, relabels, or salvages drugs.

§ 207.21 When must initial registration information be provided?

(a) Registrants must register each domestic establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug or an animal feed bearing or containing a new animal drug at such establishment.

(b) Registrants must register each foreign establishment before a drug or an animal feed bearing or containing a new animal drug manufactured, repacked, relabeled, or salvaged at the establishment is imported or offered for import into the United States.

§ 207.25 What information is required for registration?

Registrants must provide the following information:

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

(b) Each establishment's name, physical address, and telephone number(s);

(c) All name(s) of the establishment, including names under which the establishment conducts business or names by which the establishment is known;

(d) Registration number of each establishment, if previously assigned by FDA;

(e) A Unique Facility Identifier in accordance with the system specified under section 510 of the Federal Food, Drug, and Cosmetic Act.

(f) All types of operations performed at each establishment;

(g) Name, mailing address, telephone number, and email address of the official contact for the establishment, as provided in § 207.69(a); and

(h) Additionally, with respect to foreign establishments subject to registration, the name, mailing address, telephone number, and email address must be provided for:

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

(2) Each importer in the United States of drugs manufactured, repacked, relabeled, or salvaged at the establishment that is known to the establishment; and

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

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

(a) *Expedited updates.* Registrants must update their registration information no later than 30 calendar days after:

(1) Closing or selling an establishment;

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

(3) Changing the name, mailing address, telephone number, or email address of the official contact or the United States agent. A registrant, official contact, or United States agent may notify FDA about a change of information for the designated official contact or United States agent, but only a registrant is permitted to designate a new official contact or United States agent.

(b) *Annual review and update of registration information.* Registrants must review and update all registration information required under § 207.25 for each establishment.

(1) The first review and update must occur during the period beginning on October 1 and ending December 31 of the year of initial registration, if the initial registration occurs prior to October 1. Subsequent reviews and updates must occur annually, during the period beginning on October 1 and ending December 31 of each calendar year.

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

(3) If no changes have occurred since the last registration, registrants must certify that no changes have occurred.

Subpart C—National Drug Code

§ 207.33 What is the National Drug Code (NDC), how is it assigned, and what are its requirements?

(a) *What is the NDC for a drug and what products must have unique NDCs*? The NDC for a drug is a numeric code. Each finished drug product or unfinished drug subject to the listing requirements of this part must have a unique NDC to identify its labeler, product, and package size and type.

(b) *What is the format of an NDC*? (1) Except as described in paragraph (b)(4) of this section, the NDC must consist of 10 or 11 digits, divided into three segments as follows:

(i) The first segment of the NDC is the labeler code and consists of 4, 5, or 6 digits. The labeler code is assigned by FDA.

(ii) The second segment of the NDC is the product code and consists of 3 or 4 digits, as specified in paragraphs (b)(2) and (3) of this section.

(iii) The third segment of the NDC is the package code and consists of 1 or 2 digits as specified in paragraphs (b)(2) and (3) of this section. The package code identifies the package size and type of the drug and differentiates between different quantitative and qualitative attributes of the product packaging.

(2) The following combinations of labeler code, product code and package code character lengths are permissible:

(i) If a labeler code is either 5 or 6 digits in length, it may be combined with:

(A) A product code consisting of 4 digits and a package code consisting of 1 digit for a total NDC length of 10 or 11 digits (5–4–1 or 6–4–1), or

(B) A product code consisting of 3 digits and a package code consisting of 2 digits for a total NDC length of 10 or 11 digits (5–3–2 or 6–3–2).

(ii) If a labeler code is 4 digits in length, it may be combined only with a product code consisting of 4 digits and a package code consisting of 2 digits for a total NDC length of 10 digits (4–4–2).

(3) A registrant or private label distributor with a given labeler code must use only one Product-Package Code configuration (*e.g.,* a 3-digit product code combined with a 2-digit package code or a 4-digit product code combined with a 1-digit package code). This single configuration must be used in all NDCs that include the given labeler code that are reserved in accordance with § 207.33(d)(3) or listed in accordance with § 207.49 or § 207.53.

(4) An alternatively formatted NDC that is approved for use by the relevant Center Director may be used for the following HCT/Ps if they are minimally

manipulated: Hematopoietic stem/progenitor cells derived from peripheral and cord blood, and lymphocytes collected from peripheral blood.

(c) *Who must obtain an NDC labeler code and how is the code assigned and updated*? (1) Each person who engages in manufacturing, repacking, relabeling, or private label distribution of a drug subject to listing under this part must apply for an NDC labeler code, by providing the following information:

(i) The name, physical address, email address, and other contact information FDA may request, of the person for whom the NDC labeler code is requested;

(ii) The type(s) of activities (*e.g.,* manufacture or repacking) in which the person requesting the NDC labeler code engages with respect to human drugs; and

(iii) The type(s) of drug(s) (human, animal, or both, and prescription, nonprescription, or both) to which the NDC labeler code will be applied.

(2) Each person who is assigned an NDC labeler code must update the information submitted under paragraph (c)(1)of this section within 30 calendar days after any change to that information.

(d) *How is an NDC proposed for assignment by FDA, when is an NDC assigned by FDA, and how can a proposed NDC be reserved*? (1) An NDC is proposed for assignment by FDA when it is submitted for the first time with listing information in accordance with § 207.49 or § 207.53, as applicable.

(i) Each manufacturer, repacker, or relabeler must propose for assignment by FDA an NDC that includes its own labeler code for each package size and type of drug that it manufactures, repacks, or relabels for commercial distribution.

(ii) In addition, if a drug is distributed under the trade name or label of a private label distributor, the manufacturer, repacker, or relabeler must also propose for assignment by FDA an NDC that includes the labeler code of the private label distributor under whose trade name or label the drug is distributed, for each package size and type so distributed.

(2) If a proposed NDC conforms to the requirements of this section and is not reserved for a different drug or was not previously assigned to a different drug, FDA will assign the NDC to a drug when it receives listing information required for that drug under § 207.49 or § 207.53.

(3) A manufacturer, repacker, relabeler, or private label distributor may voluntarily reserve a proposed NDC for a drug, before the drug is listed, by submitting the following information:

(i) A proposed NDC that conforms to the requirements of this section;

(ii) The established name of the active ingredient(s) and the strength of each active ingredient in the drug; and

(iii) In the case of a finished drug product, the dosage form, and route of administration.

(4) If the required information is submitted and the proposed NDC is properly formatted and not already assigned or reserved, FDA will reserve the proposed NDC for a period of 2 years from the date of submission. If the drug for which the proposed NDC is reserved is not listed in accordance with § 207.49 or § 207.53 during such 2-year period, the reservation of the proposed NDC will lapse. FDA may also cancel the reservation of a proposed NDC at any time on the request of the person whose labeler code is included in the proposed NDC.

(e) *How must the information be submitted to us*? The information described in paragraphs (c) and (d) of this section must be submitted electronically unless FDA grants a waiver under § 207.65.

§ 207.35 What changes require a new NDC?

(a) Once an NDC has been assigned by FDA, the registrant must propose a new and unique NDC for a drug when there is a change, after the drug is initially marketed, to any of the information identified in paragraphs (b) and (c) of this section. A new NDC must be proposed to FDA for assignment through an updated listing in accordance with § 207.57.

(b) The proposed new NDC must include a new product code when there is a change to any of the following information:

(1) The drug's established name or proprietary name, if any;

(2) Any active pharmaceutical ingredient or the strength of any active pharmaceutical ingredient;

(3) The dosage form;

(4) A change in the drug's status, between prescription and nonprescription, or for animal drugs, between prescription, nonprescription, or veterinary feed directive (VFD) status;

(5) A change in the drug's intended use between human and animal; or

(6) The drug's distinguishing characteristics such as size, shape, color, code imprint, flavor, and scoring (if any).

(c) When there is a change only to the package size or type, including the immediate unit-of-use container, if any, the proposed new NDC must include only a new package code and retain the existing product code unless all available package codes have already been combined with the existing product code in NDCs assigned by FDA.

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

(a) A product may be deemed to be misbranded if an NDC is used:

(1) To represent a different drug than the drug for which the NDC has been assigned, as described in § 207.33;

(2) To denote or imply FDA approval of a drug; or

(3) On products that are not subject to parts 207, 607 of this chapter, or 1271 of this chapter, such as dietary supplements and medical devices.

(b) If marketing is resumed for a discontinued drug, and no changes have been made to the drug that would require a new NDC under § 207.35, the drug must have the same NDC that was assigned to it as described in § 207.33, before marketing was discontinued.

Subpart D—Listing

§ 207.41 Who must list drugs and what drugs must they list?

(a) Each registrant must list each drug that it manufactures, repacks, relabels, or salvages for commercial distribution. Each domestic registrant must list each such drug regardless of whether the drug enters interstate commerce. When operations are conducted at more than one establishment, and common ownership and control exists among all the establishments, the parent, subsidiary, or affiliate company may submit listing information for any drug manufactured, repacked, relabeled, or salvaged at any such establishment. A drug manufactured, repacked, or relabeled for private label distribution must be listed in accordance with paragraph (c) of this section.

(b) Registrants must provide listing information for each drug in accordance with the listing requirements described in §§ 207.49, 207.53, and 207.54 that correspond to the activity or activities they engage in for that drug.

(c)(1) For both animal and human drugs, each registrant must list each drug it manufactures, repacks, or relabels for commercial distribution under the trade name or label of a private label distributor using an NDC that includes such private label distributor's labeler code.

(2) Additionally, in the case of human drugs, each registrant must list each human drug it manufactures, repacks, or relabels using an NDC that includes the registrant's own labeler code, regardless of whether the drug is commercially distributed under the registrant's own label or trade name or under the label

or trade name of a private label distributor.

§ 207.45 When, after initial registration of an establishment, must drug listing information be submitted?

For each drug being manufactured, repacked, relabeled, or salvaged for commercial distribution at an establishment at the time of initial registration, drug listing information must be submitted no later than 3 calendar days after the initial registration of the establishment.

§ 207.49 What listing information must a registrant submit for a drug it manufactures?

(a) Each registrant must provide the following listing information for each drug it manufactures for commercial distribution.

(1) The appropriate NDC(s), as described in § 207.33, that include all package code variations. In the case of human drugs, the appropriate NDC(s) submitted under this paragraph include the registrant's labeler code. In the case of animal drugs, the appropriate NDC(s) submitted under this paragraph include the registrant's labeler code, except that when the drug is manufactured for commercial distribution under the trade name or label of a private label distributor, the appropriate NDC(s) for animal drugs include the private label distributor's labeler code;

(2) Package type and volume information corresponding to the package code segment of the NDC;

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

(4) The name and quantity of each active pharmaceutical ingredient in the listed drug;

(5) The name of each inactive ingredient in the listed drug, along with any assertions of confidentiality associated with individual inactive ingredients;

(6) The dosage form;

(7) The drug's approved U.S. application number, if any;

(8) The drug type (*e.g.,* as applicable, finished vs. unfinished, human vs. animal, prescription vs. nonprescription);

(9) In the case of an unfinished drug, the number assigned to the Drug Master File or Veterinary Master File, if any, that describes the manufacture of the drug;

(10) For each drug that is subject to the imprinting requirements of part 206 of this chapter including products that are exempted under § 206.7(b), the drug's size, shape, color, scoring, and code imprint (if any);

(11) The route or routes of administration of the drug;

(12) For each drug bearing an NDC:

(i) The name and Unique Facility Identifier of the establishment where the registrant who lists the drug manufactures it and the type of operation performed on the drug at that establishment, and

(ii) The name and Unique Facility Identifier of every other establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment. This includes all establishments involved in the production of each unfinished drug received by the registrant for use in the production of the drug being listed. The names, Unique Facility Identifiers, and type of operations for establishments involved in production of each unfinished drug received by the registrant for use in the production of the drug being listed may be provided by including the properly assigned and listed NDC for such unfinished drug.

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

(14) Advertisements:

(i) A representative sampling of advertisements for a human prescription drug that is not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act;

(ii) If FDA requests it, for good cause, a copy of all advertisements for a human prescription drug that is not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, including those advertisements described in § 202.1(*l*)(1) of this chapter. Such advertisements must be submitted within 30 calendar days after FDA's request.

(15) For drugs bearing the NDC(s) reported under paragraph (a)(1) of this section, except those drugs manufactured exclusively for private label distribution and not distributed under the registrant's own name and label, provide the following labeling, as applicable:

(i) *Human prescription drugs.* All current labeling except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code. This labeling submission must include the content of labeling, as defined in § 207.1(b).

(ii) *Human nonprescription drugs.* (A) For each human nonprescription drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, all current labeling, except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code. This labeling submission must include the content of labeling, as defined in § 207.1(b).

(B) For each human nonprescription drug not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), the package insert (if any), and a representative sampling of any other labeling. This labeling submission must include the content of labeling as defined in section § 207.1(b).

(iii) *Animal drugs.* (A) For each animal drug that is subject to section 512 of the Federal Food, Drug, and Cosmetic Act, which includes, but is not limited to, new animal drugs that have been approved, conditionally approved, or indexed under sections 512, 571, or 572 of the Federal Food, Drug, and Cosmetic Act, a copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), including the content of labeling as defined in § 207.1(b);

(B) For all other animal drugs, a copy of the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), the package insert, the content of labeling as defined in § 207.1(b), and a representative sampling of any other labeling;

(iv) *All other listed drugs.* For all other listed drugs, including unfinished drugs, the label (if any), except that only one representative label need be submitted where differences exist only in the quantity of contents statement.

(16) Listing submissions described in § 207.41(c)(2) for human drugs manufactured for private label distribution must include all information specified in § 207.49(a)(2) through (14) and:

(i) The appropriate NDC(s) (as described in § 207.33) that include the private label distributor's labeler code and all package code variations;

(ii) The name, mailing address, telephone number, and email address of the private label distributor; and

(iii) For drugs bearing the NDC(s) reported under paragraph (a)(16)(i) of this section, labeling as described in paragraph (a)(15) of this section that accompanies the private label distributor's product.

(b) Additionally, each registrant is requested, but not required, to provide the following information for each human drug it manufactures for commercial distribution:

(1) The drug's over-the-counter monograph reference, if any; and

(2) The date on which the drug was or will be introduced into commercial distribution.

§ 207.53 What listing information must a registrant submit for a drug that it repacks or relabels?

Each registrant must provide the following listing information for each drug it repacks or relabels:

(a) *NDC.* The appropriate NDC(s), as described in § 207.33, that include the registrant's labeler code and all package code variations;

(b) *Source NDC.* The NDC assigned to each finished drug received by the registrant for repacking or relabeling, with the exception of medical gases. Each such NDC must be associated with the corresponding NDC(s) for repacked or relabeled drugs, reported under paragraph (a) of this section.

(c) *Name and Unique Facility Identifier.* For each drug identified by an NDC reported under paragraph (a) of this section, the name and Unique Facility Identifier of every establishment where repacking or relabeling is performed for the drug and the type of operation (repacking vs. relabeling) performed at each such establishment.

(d) *Labeling.* For each drug identified by an NDC reported under paragraph (a) of this section, except those human drugs repacked or relabeled exclusively for private label distribution and not distributed under the registrant's own name and label, provide the following:

(1) *Human prescription drugs.* All current labeling for the repacked or relabeled drug except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code. This labeling submission must include the content of labeling, as defined in section § 207.1(b).

(2) *Human nonprescription drugs.* (i) For each human nonprescription drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, all current labeling, except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code. This labeling submission must include the content of labeling, as defined in § 207.1(b).

(ii) For each human nonprescription drug not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), the package insert (if any), and a representative sampling of any other labeling. This labeling submission must include the content of labeling as defined in § 207.1(b).

(3) *Animal drugs.* (i) For each animal drug that is subject to section 512 of the Federal Food, Drug, and Cosmetic Act, which includes but is not limited to, new animal drugs that have been approved, conditionally approved, or indexed under sections 512, 571, or 572 of the Federal Food, Drug, and Cosmetic Act, a copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), including the content of labeling as defined in § 207.1(b);

(ii) For all other animal drugs, a copy of the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), the package insert, the content of labeling as defined in § 207.1(b), and a representative sampling of any other labeling;

(4) *All other.* For all other listed drugs, including unfinished drugs, the label (if any), except that only one representative label need be submitted where differences exist only in the quantity of contents statement.

(e) *Advertisements.* (1) A representative sampling of advertisements for a human prescription drug that is not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act;

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

(f) *Private label distributor products.* A listing submission for a human drug distributed by a private label distributor described in § 207.41(c)(2) must include information specified in § 207.53(b) through (e) as applicable and:

(1) The appropriate NDC(s) (as described in § 207.33) that include the private label distributor's labeler code and all package code variations;

(2) The name, mailing address, telephone number, and email address of the private label distributor; and

(3) For drugs bearing the NDC(s) reported under paragraph (f)(1) of this section, labeling as described in paragraphs (d)(1) through (4) of this section, as applicable, that accompanies the private label distributor's product.

§ 207.54 What listing information must a registrant submit for a drug that it salvages?

A registrant who also relabels or repacks a drug that it salvages must list the drug it relabels or repacks in accordance with § 207.53 rather than in accordance with this section. A registrant who performs only salvaging with respect to a drug must provide the following listing information for that drug.

(a) The NDC assigned to the drug immediately before the drug is received by the registrant for salvaging;

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

(c) The name and Unique Facility Identifier for each establishment where the registrant salvages the drug.

§ 207.55 What additional drug listing information may FDA require?

For a particular listed drug, upon our request, the registrant must briefly state the basis for its belief that the drug is not subject to section 505 or 512 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act.

§ 207.57 What information must registrants submit when updating listing information and when?

Registrants must review and update listing information at a minimum, as follows:

(a) Registrants must provide listing information at the time of annual establishment registration for any drug manufactured, repacked, relabeled, or salvaged by them for commercial distribution that has not been listed previously.

(b) Registrants must review and update their drug listing information each June and December. When doing so, registrants must:

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

(ii) Submit the date that they discontinued the manufacture, repacking, relabeling or salvaging for commercial distribution of a listed drug and provide the expiration date of the

last lot manufactured, repacked, relabeled, or salvaged;

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

(iv) Submit any material changes in any information previously submitted pursuant to §§ 207.49, 207.53, 207.54, or other relevant sections of this part; or

(2) For each listed drug, certify that no changes subject to reporting under paragraph (b)(1)(iv) of this section have occurred if no such changes have occurred since the last review and update. If a drug is discontinued and FDA has received the information required under paragraph (b)(1)(ii) of this section, no further certifications are necessary for the discontinued drug. After initial electronic listing, registrants may satisfy the listing update requirement with respect to unchanged listing information by making a single ''no changes'' certification during the annual registration update under § 207.29(b) applicable to all of the registrant's listed drugs for which no changes have been made since the previous annual registration update.

(c) Registrants are encouraged to submit listing information for every drug subject to listing under this part prior to commercial distribution and are encouraged to update listing information at the time of any change affecting information previously submitted.

Subpart E—Electronic Format for Registration and Listing

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

(a) *Electronic format.* (1) Except as provided in § 207.65, all information submitted under this part must be transmitted to FDA in electronic format by using our electronic drug registration and listing system, in a form that we can process, review, and archive. We may periodically issue guidance on how to provide registration and listing information in electronic format (specifying for example method of transmission, media, file formats, preparation, and organization of files).

(2) Information provided in electronic format must comply with part 11 of this chapter, except as follows:

(i) Advertisements and labeling, including the content of labeling, required under this part are exempt from the requirements in § 11.10(a), (c) through (h), and (k) of this chapter and the corresponding requirements in § 11.30 of this chapter.

(ii) All other information submitted under this part is exempt from the requirements in § 11.10(b), (c), and (e) of this chapter and the corresponding requirements in § 11.30 of this chapter.

(b) *English language.* Drug establishment registration and drug listing information must be provided in the English language. The content of labeling must be provided at a minimum in the English language. Where § 201.15(c) of this chapter permits product labeling solely in a foreign language, the content of labeling must be submitted in that language along with an accurate English translation.

§ 207.65 How can a waiver of the electronic submission requirement be obtained?

(a) All information submitted under this part must be transmitted to FDA electronically in accordance with § 207.61(a) unless FDA has granted a request for waiver of this requirement prior to the date on which submission of such information is due. Submission of a request for waiver does not excuse timely compliance with the registration and listing requirements. FDA will grant a waiver request if FDA determines that the use of electronic means for submission of registration and listing information is not reasonable for the registrant making the waiver request.

(b) Waiver requests under this section must be submitted in writing and must include the specific reasons why electronic submission is not reasonable for the registrant and a U.S. telephone number and mailing address where FDA can contact the registrant. All waiver requests must be sent to: SPL Coordinator, U.S. Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Silver Spring, MD 20993.

(c) If FDA grants the waiver request, FDA may limit its duration and will specify terms of the waiver and provide information on how to submit establishment registration, drug listings, other information, and updates, as applicable.

Subpart F—Miscellaneous

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

(a) *Official contact.* Registrants subject to the registration requirements of this part must designate an official contact for each establishment. The official contact is responsible for:

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

(2) Reviewing, disseminating, routing, and responding to all communications from FDA including emergency communications.

(b) *United States agent.* Registrants of foreign establishments subject to this part must designate a single United States agent. The United States agent must reside or maintain a place of business in the United States and may not be a mailbox, answering machine or service, or other place where a person acting as the United States agent is not physically present. The United States agent is responsible for:

(1) Reviewing, disseminating, routing, and responding to all communications from FDA including emergency communications;

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

(3) Assisting FDA in scheduling inspections; and

(4) If FDA is unable to contact a foreign registrant directly or expeditiously, FDA may provide the information and/or documents to the United States agent. FDA's providing information and/or documents to the United States agent is equivalent to providing the same information and/or documents to the foreign registrant.

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

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

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

(c) Neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act. Registration or listing may, however, be evidence that a

facility intends to or does manufacture, repack, relabel, distribute, or salvage drugs or that a product is intended to be a drug.

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

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

(1) All establishment registration information, and

(2) After a drug is marketed, information obtained under § 207.33, § 207.49, § 207.53, § 207.54, or § 207.57.

(b) Unless such information is publicly available or FDA finds that confidentiality would be inconsistent with protection of the public health, FDA will not make publicly available:

(1) Any information submitted under § 207.55 as the basis upon which it has been determined that a particular drug is not subject to section 505 or 512 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act,

(2) The names of any inactive ingredients submitted under § 207.49(a)(4) for which the registrant makes a valid assertion of confidentiality under § 20.61 of this chapter or other provision of law, or

(3) Drug listing information obtained under § 207.33(d)(3), § 207.49(a)(9) and (12), § 207.53(b) and (c), or § 207.54(a) or (c).

(c) FDA may determine, in limited circumstances and on a case-by-case basis, that it would be consistent with the protection of the public health and the Freedom of Information Act to exempt from public disclosure specific information identified in paragraph (a) of this section.

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

■ 9. The authority citation for part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 356e, 371, 374, 379e, 379k–1.

■ 10. In § 314.81, revise paragraph (b)(3)(iv) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(iv) *Withdrawal of approved drug product from sale.* (*a*) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are manufacturers, repackers, or relabelers subject to part 207 of this chapter must submit the following information about the drug, in accordance with the applicable requirements described in §§ 207.61 and 207.65:

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

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

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

(*4*) The date on which the drug is expected to be no longer in commercial distribution. FDA requests that the reason for withdrawal of the drug from sale be included with the information.

(*b*) Within 30 calendar days of the withdrawal of an approved drug from sale, applicants who are not subject to part 207 of this chapter must submit the information listed in paragraphs (b)(3)(iv)(*a*)(*1*) through (*4*) of this section. The information must be submitted either electronically or in writing to the Drug Registration and Listing Office, Food and Drug Administration, Center for Drug Evaluation and Research.

(*c*) Reporting under paragraph (b)(3)(iv)(*a*) of this section constitutes compliance with the requirements of § 207.57 of this chapter to update drug listing information with respect to the withdrawal from sale.

* * * * *

§ 314.125 [Amended]

■ 11. Amend § 314.125 in paragraph (b)(11) by removing the words ''or processed''.

PART 514—NEW ANIMAL DRUG APPLICATIONS

■ 12. The authority citation for part 514 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 354, 356a, 360b, 360ccc, 371, 379e, 381.

■ 13. In § 514.111 add paragraph (a)(12) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

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

* * * * *

PART 515—MEDICATED FEED MILL LICENSE

■ 14. The authority citation for part 515 continues to read as follows:

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

§ 515.10 [Amended]

■ 15. In § 515.10(b)(8), remove the phrase ''§§ 207.20 and 207.21'' and add in its place the phrase ''part 207''.

PART 601—LICENSING

■ 16. The authority citation for part 601 continues to read as follows:

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

■ 17. In § 601.2, add paragraph (f) to read as follows:

§ 601.2 Applications for biologics licenses; procedures for filing.

* * * * *

(f) *Withdrawal from sale of approved biological products.* A holder of a biologics license application (BLA) must report to FDA, in accordance with the requirements of §§ 207.61 and 207.65, the withdrawal from sale of an approved biological product. The information must be submitted to FDA within 30 working days of the biological product's withdrawal from sale. The following information must be submitted: The holder's name; product name; BLA number; the National Drug Code; and the date on which the product is expected to be no longer in commercial distribution. The reason for the withdrawal of the biological product is requested but not required to be submitted.

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

■ 18. The authority citation for part 607 continues to read as follows:

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

■ 19. Revise the heading for part 607 to read as set forth above.

■ 20. Add § 607.1 to subpart A to read as follows:

§ 607.1 Scope.

(a) This part establishes establishment registration and product listing requirements for manufacturers of human blood and blood products.

(b) This part establishes establishment registration and product listing requirements for manufacturers of products that meet the definition of a device under the Federal Food, Drug, and Cosmetic Act and that are licensed under section 351 of the Public Health

Service Act, as well as licensed biological products used in the manufacture of a licensed device.

■ 21. In § 607.3 revise the second sentence in paragraph (b) and add paragraphs (k) and (*l*) to read as follows:

§ 607.3 Definitions.

* * * * *

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

* * * * *

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

(*l*) *Foreign* for the purpose of registration and listing under this part when used to modify the term ''establishment'' refers to an establishment that is located in a foreign country and is the site where a blood product that is imported or offered for import into the United States was manufactured.

■ 22. Revise § 607.7 to read as follows:

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

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

■ 23. In § 607.20 revise the first sentence in paragraph (c) to read as follows:

§ 607.20 Who must register and submit a blood product list.

* * * * *

(c) Except in the case of licensed device manufacturers, no registration fee is required. * * *

■ 24. In § 607.21 revise the last sentence to read as follows:

§ 607.21 Times for establishment registration and blood product listing.

* * * Owners or operators of all establishments so engaged must register annually between October 1 and December 31 and must update their blood product listing every June and December.

■ 25. Revise § 607.22 to read as follows:

§ 607.22 How to register establishments and list blood products.

(a) Initial and subsequent registrations and product listings must be submitted electronically through the Blood Establishment Registration and Product Listing system, or any future superseding electronic system. This information must be submitted in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e), and the corresponding requirements in § 11.30. All information submitted under this part must be transmitted to FDA electronically unless FDA has granted a request for waiver of this requirement prior to the date on which the information is due. Submission of a request for waiver does not excuse timely compliance with the registration and listing requirements. FDA will grant a waiver request if FDA determines that the use of electronic means for submission of registration and listing information is not reasonable for the registrant making the waiver request.

(b) Waiver requests under this section must be submitted in writing and must include the specific reasons why electronic submission is not reasonable for the registrant and a U.S. telephone number and mailing address where FDA can contact the registrant. All waiver requests must be sent to the Director of FDA's Center for Biologics Evaluation and Research through the Document Control Center (see addresses *in* § 600.2).

(c) If FDA grants the waiver request, FDA may limit its duration and will specify terms of the waiver and provide information on how to submit establishment registration, drug listings, other information, and updates, as applicable.

■ 26. Revise § 607.25 to read as follows:

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

(a) The Blood Establishment Registration and Product Listing system requires furnishing or confirming registration information required by the Federal Food, Drug, and Cosmetic Act. This information includes the name and street address of the establishment, including post office code; a registration number if previously assigned by FDA and a Unique Facility Identifier in accordance with the system specified under section 510 of the Federal Food, Drug, and Cosmetic Act; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned partnership, or corporation); and the name of the owner or operator of such establishment. The term ''name of the owner or operator'' must include, 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 information required must be given separately for each establishment, as defined in § 607.3(c).

(b) The following information must also be provided:

(1) A list of blood products by established name as defined in section 502(e) of the Federal Food, Drug, and Cosmetic Act and by proprietary name, if any, which are being manufactured for commercial distribution at the identified establishment and which have not been included in any list previously submitted to FDA through the Blood Establishment Registration and Product Listing system or any future superseding electronic system.

(2) For each blood product so listed that is subject to section 351 of the Public Health Service Act, the license number of the manufacturer issued by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(3) For each blood product listed, the registration number if previously assigned by FDA and the Unique Facility Identifier of the parent establishment. An establishment not owned, operated, or controlled by another firm or establishment is its own parent establishment.

■ 27. In § 607.26 revise the first sentence to read as follows:

§ 607.26 Amendments to establishment registration.

Changes in individual ownership, corporate or partnership structure, location, or blood product handling activity must be submitted electronically through the Blood Establishment Registration and Product Listing system, or any future superseding electronic system, as an amendment to registration within 5 calendar days of such changes. * * *

■ 28. In § 607.30 revise the introductory text of paragraph (a) to read as follows:

§ 607.30 Updating blood product listing information.

(a) After submission of the initial blood product listing information, every person who is required to list blood products under § 607.20 must submit electronically through the Blood Establishment Registration and Product

Listing system, or any future superseding electronic system, at a minimum once in June and December of every year, the following information:

* * * * *

■ 29. Revise § 607.35 to read as follows:

§ 607.35 Blood product establishment registration number.

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

■ 30. Revise § 607.37 to read as follows:

§ 607.37 Public disclosure of establishment registration and blood product listing information.

(a) Except as provided in paragraph (b) of this section, all registration and listing information obtained under §§ 607.25, 607.26, and 607.30 will be made available for public disclosure through the Center for Biologics Evaluation and Research (CBER) Blood Establishment Registration Database Web site by using the CBER electronic Web-based application or by going in person to the Food and Drug Administration, Division of Freedom of Information Public Reading Room (see addresses in § 20.120(a) of this chapter).

(b) FDA may find, in limited circumstances and on a case-by-case basis, that it would be consistent with the protection of the public health to exempt from public disclosure specific listing information obtained under § 607.25 or § 607.30.

(c) Other requests for information regarding blood establishment registrations and blood product listings should be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research Office of Communication, Outreach, and Development, 10903 New Hampshire Ave., Bldg. 71, Rm. 3103, Silver Spring, MD 20993–0002.

■ 31. Revise § 607.39 to read as follows:

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

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

■ 32. In § 607.40 revise paragraphs (d) introductory text and (d)(3) and add paragraph (e) to read as follows:

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

* * * * *

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

* * * * *

(3) The foreign establishment or the United States agent must report changes in the United States agent's name, address, telephone number, or email address to FDA within 30 calendar days of the change.

(e) Each foreign establishment required to register under paragraph (a) of this section must register and list blood products using the Blood Establishment Registration and Product Listing system, or any superseding electronic system, unless FDA waives the electronic submission requirement in accordance with § 607.22.

■ 33. In § 607.65 add paragraph (g) to read as follows:

§ 607.65 Exemptions for blood product establishments.

* * * * *

(g) Persons who engage solely in the production of any plasma derivative, including, but not limited to, albumin, Immune Globulin, Factor VIII and Factor IX, bulk product substances such as fractionation intermediates or pastes, or recombinant versions of plasma derivatives or animal derived plasma derivatives. These persons must register and list under part 207 of this chapter.

■ 34. Add subpart E, consisting of § 607.80, to part 607 to read as follows:

Subpart E—Establishment Registration and Product Listing Of Licensed Devices

§ 607.80 Applicability of part 607 to licensed devices.

Manufacturers of products that meet the definition of a device under the Federal Food, Drug, and Cosmetic Act and that are licensed under section 351 of the Public Health Service Act, as well as licensed biological products used in the manufacture of a licensed device, must register and list following the procedures under this part, with respect to their manufacture of those products, unless otherwise noted in this section.

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

■ 35. The authority citation for part 1271 continues to read as follows:

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

§ 1271.1 [Amended]

■ 36. Amend § 1271.1 in paragraphs (a) and (b)(2) by removing ''207.20(f)'' and adding in its place ''207.9(a)(5)''; in paragraph (a) by removing the term ''a unified'' and adding in its place the term ''an electronic''; and in paragraph (b)(2) by removing the phrase ''in subpart B of this part'' and adding in its place the phrase ''in part 207 (if a drug and/or biological product) of this chapter or part 807 (if a device) of this chapter''.

■ 37. In § 1271.3 add paragraphs (mm) and (nn) to read as follows:

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

* * * * *

(mm) *Importer* means a company or individual in the United States that is the owner, consignee, or recipient, at the time of entry, of the foreign establishment's HCT/P that is imported into the United States.

(nn) *United States agent* means a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. This definition excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present.

§ 1271.20 [Amended]

■ 38. Amend § 1271.20 by removing ''207.20(f)'' and adding in its place ''207.9(a)(5)'' and by removing the phrase ''subparts B, C, and D of this part'' and adding in its place ''subparts C and D of this part''.

■ 39. Revise § 1271.22 to read as follows:

§ 1271.22 How do I register and submit an HCT/P list?

(a) You must use the electronic registration and listing system at *http://www.fda.gov/cber/tissue/tisreg.htm* in accordance with § 1271.25 for:

(1) Establishment registration,

(2) HCT/P listings, and

(3) Updates of registration and HCT/P listing.

(b) FDA will periodically issue guidance on recommended procedures for providing registration and listing information in electronic format (for

example, method of transmission, media, file formats, preparation, and organization of files).

(c) You must provide the information under paragraph (a) of this section in accordance with part 11 of this chapter, except for the requirements in § 11.10(b), (c), and (e) and the corresponding requirements in § 11.30.

■ 40. Add § 1271.23 to subpart B to read as follows:

§ 1271.23 How is a waiver from the electronic format requirements requested?

(a) You may request a waiver from the requirement in § 1271.22 that information must be provided to FDA in electronic format. Submission of a request for waiver does not excuse timely compliance with the registration and listing requirements. FDA will grant a waiver request if FDA determines that the use of electronic means for submission of registration and listing information is not reasonable for the registrant making the waiver request.

(b) Waiver requests under this section must be submitted in writing and must include the specific reasons why electronic submission is not reasonable for the registrant and a U.S. telephone number and mailing address where FDA can contact the registrant. Waiver requests may be sent to the Center for Biologics Evaluation and Research (CBER), Document Control Center (see addresses in § 600.2 of this chapter).

(c) If FDA grants the waiver request, FDA may limit its duration and will specify terms of the waiver and provide information on how to submit establishment registration, listings, other information, and updates, as applicable.

■ 41. In § 1271.25 revise paragraphs (a) introductory text and (a)(2) and (3), add paragraphs (a)(5) and (6), revise paragraph (c)(4), and add paragraph (d) to read as follows:

§ 1271.25 What information is required for establishment registration and HCT/P listing?

(a) Your establishment registration must include:

* * * * *

(2) Each physical location, including the street address, telephone number, email address, and the postal service ZIP code of the establishment;

(3) The name, address, telephone number, email address, and title of the reporting official;

* * * * *

(5) Each foreign establishment must also submit the name, address, telephone number, and email address of each importer that is known to the establishment, and the name of each person who imports or offers for import such HCT/P to the United States for purposes of importation; and

(6) Each foreign establishment must also submit the name, address, telephone number, and email address of its United States agent.

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

(ii) Upon request from FDA, the United States agent must assist FDA in communications with the foreign establishment, respond to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and assist FDA in scheduling inspections of the foreign establishment. If the Agency is unable to contact the foreign establishment directly or expeditiously, FDA may provide information or documents to the United States agent, and such an action is equivalent to providing the same information or documents to the foreign establishment.

(iii) The foreign establishment or the United States agent must report changes in the United States agent's name, address, telephone number, or email address to FDA within 30 calendar days of the change.

* * * * *

(c) * * *

(4) Any material change in any information previously submitted. Material changes include any change in registration and listing information, submitted, such as whether the HCT/P meets the criteria set out in § 1271.10.

(d) If your HCT/P is described under § 1271.20 and is regulated under a BLA, you must submit the information required under part 207 of this chapter using the procedures under subpart E of part 207.

■ 42. Revise § 1271.26 to read as follows:

§ 1271.26 When must I amend my establishment registration?

If the ownership or location of your establishment changes, or if there is a change in the United States agent's name, address, telephone number, or email address, you must submit an amendment to registration within 30 calendar days of the change.

Dated: August 22, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–20471 Filed 8–30–16; 8:45 am]

BILLING CODE 4164–01–P