

- The drug's or active pharmaceutical ingredient's established name and proprietary name (if any). The established name (sometimes referred to as generic name) is ordinarily either the drug's compendial name or, if there is no compendial name, the drug's common or usual name. The proprietary name (sometimes referred to as trade name) is generally the drug's marketed or advertised name as designated by the manufacturer, repacker, relabeler, or private label distributor. Most consumers recognize a drug by its proprietary name rather than its established name. Proposed § 207.33(c) and (d) would require submission of these names because knowing a drug's established name would let us determine, for example, which companies market identical drugs and which drugs can be substituted in the event of drug shortages or recalls. Knowing a drug's proprietary name would enable us to identify a drug to the public during a recall or consumer alert. This information is currently required under § 207.25(b)(1) and is submitted on Form FDA 2657.

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

- Name and quantity of each active pharmaceutical ingredient in a drug. Proposed § 207.33(c)(2) and, if applicable, proposed § 207.33(c)(3), would require manufacturers to submit this information to us (unless the approved U.S. application number is provided). Knowing the name and quantity of a drug's active pharmaceutical ingredients would help us assign unique product codes and help ensure that the assigned NDC numbers are unique to different products. For example, assume that a manufacturer makes a drug in two different strengths, 100 milligrams (mg) and 500 mg. If we only required the manufacturer to identify the active pharmaceutical ingredient, we might assume, incorrectly, that the manufacturer made two versions of the same drug in the same strength and then assign the same product code to both drugs. Instead, by proposing to require information about the quantity of the drug's active pharmaceutical ingredient, we would be able to assign one product code to the 100 mg product and a different product code to the 500 mg product. As an alternative to providing the name and quantity of the drug's active pharmaceutical ingredient, proposed § 207.33(c)(2) would allow a manufacturer to give us the drug's approved U.S. application number; the approved U.S. application number would allow us to link the drug to a particular application and determine the name and quantity of the active pharmaceutical ingredients in that drug.

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

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

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

- Name of the inactive ingredient(s). Proposed § 207.33(c)(2), and, if applicable, (c)(3) would require manufacturers to give us the drug's approved U.S. application number or, in the alternative, the name of each inactive ingredient for each human and animal drug that the manufacturer regards as subject to section 505 or section 512 of the act or section 351 of the PHS Act, and for each human OTC drug that the manufacturer regards as not subject to section 505 of the act, and whether the name of an inactive ingredient falls under § 20.61 or is otherwise prohibited from disclosure and, if so, why. Proposed § 207.33(c)(3) describes the requirements of the manufacturer who is manufacturing a drug for a private label distributor. Such manufacturers would be required to give us the name of each inactive ingredient for certain drugs, as described previously, or the drug's U.S. approved application number for the drug it manufactures for a private label distributor. Proposed § 207.33(c)(2) and (c)(3) are authorized under section 510 of the act as well as other provisions. We are considering whether to require the name of each inactive ingredient to be submitted for other categories of drugs as well.

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

- Package size and type. Proposed § 207.33(c)(1), (c)(2), (c)(3) (if applicable), (d)(1), and (d)(2) would require manufacturers and repackers respectively to provide information about

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

- Marketing status. Proposed § 207.33(c)(2) and, if applicable, (c)(3), would require manufacturers to tell us whether the drug is available only by prescription or is available OTC. Having such information in our electronic database would enable us to determine quickly which drugs are available by prescription and which are OTC. In addition, some entities that rely on NDC numbers, such as CMS and health care insurance companies, might treat prescription drugs differently from OTC drugs. For example, an insurer might reimburse consumers for prescription drug expenses, but not for OTC drug expenses. The drug's marketing status--whether prescription or OTC--is currently submitted on Form FDA 2657.

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

- Imprinting information. For each drug product subject to the listing requirements and covered under § 206.1, including products that are exempted under § 206.7(b), manufacturers must provide the size, shape, color, and code imprint (if any) (proposed § 207.33(c)(2)(vii) and, if applicable, proposed § 207.33(c)(3)). This provision is similar to current § 207.25(c), except the current provision also requires that the name of the drug product, its active ingredient(s), dosage strength, NDC number, and the name of its manufacturer or distributor be submitted. Under the proposal, the name of the drug product, its active ingredient(s) (proposed § 207.33(c)(2) uses the term "active pharmaceutical ingredient"), and dosage strength (proposed § 207.33(c)(2) uses the term "dosage form") would be submitted to us under proposed § 207.33(c) along with the imprinting information. The NDC number would be submitted under proposed § 207.49 for listing, the name of the private label distributor would be submitted under proposed §§ 207.33 and 207.49 for listing, and the name of the manufacturer would be submitted under proposed § 207.25 for registration. All of this information would be accessible via our

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

- NDC number assigned to the drug immediately before the repacker or relabeler received that drug. Proposed § 207.33(d) would require repackers and relabelers to give us the NDC number of the drug that they receive. This information would enable us to link that drug to a particular source and, as we said earlier in this part, eliminate the need for repackers and relabelers to obtain certain drug information from those sources to obtain an NDC number. For example, assume that relabeler Alpha received drug X from manufacturer Beta. If Alpha gives us the NDC number for drug X, we will then be able to link Alpha's relabeled drug to Beta. We would also eliminate any need for Alpha to ask Beta for information about drug X for purposes of getting an NDC number and eliminate the possibility that Alpha might report incorrect or contradictory information about drug X compared to the information given to us by Beta.
- Type of operation. Proposed § 207.33(d) would require repackers and relabelers to report the type of operation (that is, repacking or relabeling) performed for a drug. This information is comparable to the information we currently receive about an establishment's "type of business" on Form FDA 2657, except that proposed § 207.33(d) is limited to repackers and relabelers.
- Information regarding private label distributors. Proposed § 207.33(c)(3) and 207.33(d)(2) would require manufacturers, repackers, and relabelers who manufacture, repack, or

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

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

iii. Types of changes that would require a new NDC number. Proposed § 207.33(f) would describe the types of changes in information that would require a new NDC number. In brief, proposed § 207.33(f)(1) would require a new NDC number for any change of information that would be required under proposed § 207.33(c) and (d), except for the following contact information: Name; address; telephone and fax numbers; and e-mail address for the manufacturer, repacker, relabeler, or private label distributor. In addition, § 207.33(f)(2) requires manufacturers to obtain a new NDC number when there is a change in an inactive ingredient for each human prescription drug that the manufacturer regards as not subject to section 505 of the act and for each animal drug that the manufacturer regards as not subject to section 512 of the act. Although we are not proposing to require, at this time, that manufacturers submit the name

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of each inactive ingredient to us when they obtain an NDC number for these drugs, we are proposing to require that manufacturers notify us only of the fact that there has been a change in an inactive ingredient for these drugs. This would ensure that a unique NDC number is assigned to these drugs when the drug's inactive ingredient(s) has changed. It is important that marketed drugs have unique NDC numbers that are accurate because, as discussed in section IV.C.2 of this document, NDC numbers are an important, standardized, identification system for drug products and are used for many purposes. In addition, identifying marketed drugs in our electronic database for which inactive ingredients have changed would help us investigate, as discussed in section IV.C.3 of this document, incidents of allergic reactions in patients as well as possible drug contamination, counterfeiting, or adulteration. Although we are not proposing it at this time, we are considering requiring in the future that manufacturers submit the name of each inactive ingredient to obtain an NDC number for categories of drugs beyond those referenced in proposed § 207.33(c)(2)(ii) and 207.33(c)(3). We are specifically requesting comments on the feasibility of submitting these inactive ingredients. The proposed rule would be similar to current § 207.35(b)(4)(i), which requires a registrant to assign a new NDC number if any change occurs in a product's characteristics that clearly distinguishes one drug product version from another. However, proposed § 207.33(f) would differ from the current requirement in several important respects. First, proposed § 207.33(f) would require changes to be reported to us in accordance with proposed § 207.33(e) (which would require electronic submission of information) and § 207.33(g) (which describes timing requirements discussed later in this part). The current regulation has no comparable electronic reporting requirement. Second, proposed § 207.33(f) would not require us to publish a notice in the FEDERAL REGISTER announcing our determination as to whether a change requires assignment of a new product code. Because

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the proposed rule would create an electronic drug registration and listing system and have us assign NDC numbers quickly that would be accessible in the registration and listing database, we find it unnecessary and impractical to publish FEDERAL REGISTER notices regarding product code changes. Third, although current § 207.35(b)(4)(i) allows registrants to assign their own package codes for changes involving trade packages, proposed § 207.33(f) would eliminate this provision because we would assign the new NDC number ourselves to ensure that the NDC number is unique and that our NDC number database is accurate and up-to-date. Fourth, proposed § 207.33(f), in conjunction with proposed § 207.33(c) and (d), gives a more complete description of which changes would require a new NDC number, compared with current § 207.25(b)(4)(i) (which currently lists examples of changes). Because manufacturers, repackers, and relabelers currently have different practices with respect to assigning NDC numbers, this change would eliminate inconsistency and would introduce an element of certainty with respect to the assignment of new NDC numbers.

iv. When the information would be provided. Proposed § 207.33(g) would explain when a manufacturer, repacker, or relabeler must provide the information to obtain an NDC number. In brief, the proposal would require a manufacturer, repacker, or relabeler to provide the information described in proposed § 207.33(c), (d), and (f) either before or at the time drug listing information is required under proposed §§ 207.45 or 207.57. (We discuss proposed §§ 207.45 and 207.57 later in this document.) The proposed requirement differs slightly from current §§ 207.21(b), 207.22(b), and 207.25(b)(8), which allows manufacturers, repackers, and relabelers to give us NDC numbers as part of their drug listing information, because the proposal would allow companies to give us information earlier than the drug listing process would be completed. This ability to seek NDC numbers throughout the year should help us keep the

National Drug Code Directory current and, as a result, provide more accurate and useful NDC number information to entities that rely on or use NDC numbers. In addition, the proposed scheme would give manufacturers, repackers, and relabelers more flexibility to obtain an NDC number earlier for their own planning purposes. Furthermore, we will know which NDC number corresponds to a drug immediately because we will assign it, rather than the current system where manufacturers, repackers, and relabelers assign their own NDC numbers and only report those numbers to us as part of their drug listing information.

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

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

Proposed § 207.37(a) would state that an NDC number must not be used to represent a different drug than the drug to which it was assigned. This restriction would prevent manufacturers, for example, from using the same NDC number for different drugs and thus prevent potential discrepancies among databases that rely on or use NDC numbers to distinguish between drugs. The restriction would prevent two different drugs from having the same NDC

number and avoid medication errors that could result if the NDC number encoded in a bar code represented more than one drug. Use of an NDC number not assigned to a drug would also cause a drug to be misbranded under section 502(a) of the act because the drug's label would be misleading.

Proposed § 207.37(b) would state that a different NDC number must not be used if marketing is resumed for a drug that was discontinued earlier. If marketing is resumed for a drug, and no changes have been made to the drug that would require a new NDC number under § 207.33(f), the drug must have the same NDC number that was assigned to it earlier before marketing was discontinued. This would prevent two NDC numbers from being assigned to or used for the same drug. Consistent with this rationale, proposed § 207.37(b) would revoke current § 207.35(b)(4)(ii), which states that the product code of a discontinued product may be reassigned to another product 5 years after the expiration date of the discontinued product or, if there is no expiration date, 5 years after the last shipment of the discontinued product into commercial distribution.

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

Proposed § 207.37(d) would state that NDC numbers must not be used on products that are not subject to the drug listing requirements of part 207, such as dietary supplements and medical devices. We are proposing this requirement because the fundamental purpose behind

NDC numbers was to establish an identification system to help in the automated processing of drug data and claims. Use of NDC numbers on non-drug products could introduce misleading information in databases, lead to inappropriate claims processing, and undermine the accuracy and reliability of an NDC system. For example, some human dietary supplements bear an NDC number on their labels. FDA considers a human dietary supplement that bears an NDC number misbranded under 21 U.S.C. 343(a)(1), which provides that a food is misbranded if its labeling is false or misleading in any particular. A product labeled and marketed as a human dietary supplement is not a drug listed with FDA; thus, the presence of an NDC number on the label is a false representation about the nature of the product.

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

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

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

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

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b. When would we expect NDC numbers to appear on drug labels? Although current regulations do not require NDC numbers on drug labels (other than NDC numbers encoded in a bar code, where such bar codes are required under current § 201.25), almost all human and animal prescription drugs already have NDC numbers on their labels because government agencies and third-party payers rely on NDC numbers for reimbursement and other purposes. Thus, when we issue a final rule requiring NDC numbers to appear on drug labels, such a requirement should have little impact on human and animal prescription drug labels.

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

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

We are considering shortening the compliance dates by which the appropriate NDC number must appear on drug labels to 2 years after the effective date of a final rule for prescription drugs and 5 years after the effective date of a final rule for OTC drugs. We discuss this issue further in section VI of this document. We invite comment on whether a shorter implementation period would be preferable.

These implementation periods would permit manufacturers, repackers, and relabelers to incorporate the appropriate NDC number at minimal additional cost when redesigning their

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

We invite comments on the implementation scheme described here.

#### D. Listing

##### 1. Who Would Be Required To List Drugs?

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

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

Under current § 207.20(a), such drugs must be listed whether or not they enter interstate commerce. This is consistent with Congress's intention for section 510 of the act to apply to drugs both in interstate and intrastate commerce as stated in section 301 of Public Law 82-781, in part, as follows:

[T]he products of all [establishments in which drugs are manufactured, prepared, propagated, compounded, or processed] are likely to enter the channels of interstate commerce and directly affect such commerce; and \* \* \* the regulation of interstate commerce in drugs without provision for registration and inspection of establishments that may be engaged only in intrastate commerce in such drugs would discriminate against and depress interstate commerce in such drugs, and adversely burden, obstruct, and affect such interstate commerce.

Proposed § 207.41(a) also provides that when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments, listing information may be submitted by the parent, subsidiary, and/or affiliate company for drugs at all establishments. This provision would also apply when operations are conducted at both domestic and foreign establishments and there exists joint ownership and control among all the establishments. This provision is consistent with current § 207.20(a).

Under proposed § 207.41(a), drug product salvagers would be required to list. As discussed in sections IV.A.5 and IV.B.1 of this document, and consistent with current

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

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

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

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

We are proposing to alter the arrangement permitted under current § 207.20(b). Although we recognize that this proposed shift in responsibility may alter current business practices, we

believe that proposed § 207.41(c) will help to ensure that listing information is more accurate and complete. The current scheme has caused confusion and resulted in inaccurate and incomplete listing information. Some private label distributors that have elected to list their drugs have not had access to all the information needed to list the drugs accurately. Some private label distributors have claimed that manufacturers, repackers, and relabelers have been reluctant to provide certain information to them. In addition, in some instances, the parties have been uncertain about who is responsible for listing.

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

reabeled, or salvaged for a private label distributor, manufacturers, repackers, relabelers, and drug product salvagers would have to obtain any existing NDC number from the private label distributor or would have to obtain the NDC number from FDA for a drug distributed by a private label distributor. Manufacturers, repackers, relabelers, and drug product salvagers would have to place the NDC number assigned to the private label distributor's drug on the label. We specifically invite comments on this proposed change in the listing responsibilities of manufacturers, repackers, relabelers, drug product salvagers, and private label distributors and its potential effect on business practices.

## 2. When Would Initial Listing Information Be Provided?

Under proposed § 207.45, manufacturers, repackers, relabelers, and drug product salvagers would list, at the time of initial registration of an establishment, any drug being manufactured, repacked, relabeled, or salvaged for commercial distribution at that establishment. This provision is consistent with section 510(j)(1) of the act, which requires, among other things, that every person who registers with the Secretary under sections 510(b), (c), (d), or (i) of the act must list drugs that are being manufactured, prepared, propagated, compounded, or processed for commercial distribution. Proposed § 207.45 pertains to the submission of listing information for drugs at the time of the initial registration of an establishment. Reviewing and updating information for drugs already listed and providing listing information for drugs not previously listed are covered under proposed § 207.57. Proposed § 207.57 is discussed in section IV.D.8 of this document.

## 3. What Listing Information Would Be Required?

To list a drug, manufacturers would be required to provide the information in proposed § 207.49, repackers and relabelers would be required to provide the information in proposed

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

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

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

- NDC number;
- Route of administration;
- Approved U.S. application number or approved U.S. BLA number, if any;
- Registration number of each establishment where the manufacturing is performed for the drug;
- Schedule of the drug under section 202 of the Controlled Substances Act (21 U.S.C. 812);

- With respect to foreign establishments only, the name and contact information of each importer of the drug and of each person who imports or offers for import the drug;

- Labeling;
- Advertisements; and
- Information about the private label distributor, if any.

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

- NDC number;
- Registration number of each establishment where the repacking or relabeling is performed for the drug;

- With respect to foreign establishments only, the name and contact information of each importer of the drug and of each person who imports or offers for import the drug;

- Labeling;
- Advertisements; and
- Information about the private label distributor, if any.

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

- NDC number assigned to the drug immediately before the drug is received by the drug product salvager;
- Lot number and expiration date of the salvaged drug;

- Registration number of each establishment where the drug product salvager salvages the drug;

- With respect to foreign establishments only, the name and contact information of each importer and of each person who imports or offers for import the drug; and

- Information about the private label distributor, if any.

#### 4. What Listing Information Would Be Required for Manufacturers?

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

a. NDC number. For a drug to be considered listed, manufacturers and, as discussed below, repackers, relabelers, and drug product salvagers, must submit the NDC number for the drug as part of the drug's listing information.<sup>7</sup> The NDC number, including the information that would be submitted to us to obtain an NDC number, is explained under proposed § 207.33. Knowing the NDC number of the drug would enable us to incorporate by reference information about the drug submitted by the manufacturer, repacker, or relabeler to obtain an NDC number under proposed § 207.33(c) and (d), as well as information submitted by the manufacturer, repacker, or relabeler to list the drug. This would reduce the amount of information that must be provided to us by manufacturers, repackers, relabelers, and drug product salvagers for listing. Current § 207.25(b)(8) requires the submission of the NDC number for each drug listed, and this information is currently submitted on Form FDA 2657.

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

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

c. Approved U.S. application number. The approved U.S. application number or the approved U.S. BLA number,<sup>8</sup> if any, would enable us to link to the information about the drug that was already submitted to us for marketing approval. Section 510(j)(1)(A) of the act requires the submission of a reference to the authority for marketing a drug subject to section 505 or 512 of the act. In addition, current § 207.25(b)(2) requires the submission of the application number for each drug listed that the registrant regards as subject to section 505 or 512 of the act. The drug's application number is currently submitted on Form FDA 2657. As discussed in section IV.D.4.g of this document, if the approved U.S. application number is provided to us when a human prescription or OTC drug is listed, the manufacturer would not be required to re-submit the labeling for the approved drug. The application number would incorporate by reference the labeling for approved drugs. This would eliminate unnecessary duplication of effort and cost to industry. The application number may have already been provided under § 207.33(c)(2)(i) and (c)(2)(ii) instead of providing the names of the active pharmaceutical ingredient and the inactive ingredient. If so, it will already be in our database and would not need to be resubmitted.

d. Registration number of each establishment. The registration number of each establishment where the manufacturing is performed for the drug would enable us to identify the establishment where the drug is manufactured. This would help our investigators better prepare for inspections and collect postmarketing surveillance samples. Although this information would

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

already be submitted for registration under proposed § 207.25(e), submitting it at listing would enable us to link this information to the drug being listed. Current § 207.25(b)(7) requires, for each drug listed, the submission of the registration number of each drug establishment at which the drug is manufactured or processed (within the meaning of current § 207.3(a)(8)). Current § 207.25(b)(3) requires the submission of the license number of the manufacturer of drugs subject to section 351 of the PHS Act. The "establishment registration number" is defined in proposed § 207.1 to mean the number assigned by FDA to the establishment during the establishment registration process. Currently, we plan to assign the FEI number as the establishment registration number. In the future, however, we may use a different number as the establishment registration number. The establishment registration number is currently submitted on Form FDA 2657.

e. Schedule of the drug. The schedule of the drug under section 202 of the Controlled Substances Act would enable us to provide yearly estimates of medical, scientific, and reserve stock needs for Schedule I and II substances (21 CFR part 1303, 21 U.S.C. 826). Under section 302(a) of the PHS Act (42 U.S.C. 242(a)), the Secretary is responsible for providing to the Drug Enforcement Administration estimates of the quantities of controlled substances for which production quotas must be established that will be required to meet the legitimate medical, scientific, and reserve stock needs of the United States for the following calendar year. The schedule of the drug is currently submitted on Form FDA 2657.

f. Information about each importer of the drug and each person who imports or offers for import the drug to the United States. Foreign establishments only must provide the name, address, telephone and fax numbers, and e-mail address of each importer of such drug in the United States that is known to the establishment, and of each person who imports or offers for

import such drug to the United States. As discussed under section IV.B.3 of this document, the term "known to" would mean any importer that is known to the foreign establishment as well as any importer that the foreign establishment has reason to know of. We therefore expect that the person responsible for completing the required registration forms on behalf of the foreign establishment would undertake appropriate due diligence in completing those forms, including to find out and report importers that others in his or her establishment know of or have reason to know of. Foreign establishments would provide this information for listing unless previously provided under proposed § 207.25(h) for registration. The Bioterrorism Act requires foreign establishments to submit, among other things, the name of each importer of each drug that is known to the establishment, and the name of each person who imports or offers for import each drug to the United States for purposes of importation. The Bioterrorism Act requires submission of such information as part of registration information and also specifically requires listing information to be submitted for each drug being manufactured for commercial distribution (see section IV.A.4.d of this document). We are proposing, under this part, to make the submission of information concerning importers of drugs and persons who import or offer for import drugs to the United States both a registration and a listing requirement. However, if the information has been previously provided by the foreign establishment at registration, the foreign establishment would not be required to re-enter that information into the database at listing. Our listing database will be populated automatically with the required information. This would reduce the amount of information that must be provided to us by the foreign establishment at listing. The information about each importer of the establishment's drug that is known to the establishment and each person who imports or offers for import the drug to the United States is

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not currently required to be submitted under current part 207 or on Form FDA 2656 or Form FDA 2657.

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

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

Under proposed § 207.49(g)(1) and, as discussed below under proposed §§ 207.49(g)(2) and 207.49(g)(3), only one representative container or carton label would be submitted where differences exist only in the quantity of contents statement or the bar code. This proposed provision is consistent with current § 207.25(b)(2), although the proposal would add differences in the bar code to the provision. This provision would reduce the number of labels that must be submitted to us by the manufacturer.

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

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

The labeling submission requirements in proposed § 207.49(g) are almost identical in substance to the labeling submission requirements of current § 207.25(b)(2) through (b)(5), except that manufacturers would also be required, as discussed previously, to submit electronically the "content of labeling." In addition, the labeling submission requirements in proposed § 207.49(g) conform to the statutory requirements of section 510(j) of the act. The proposed requirement to submit labeling, including the content of labeling, for human prescription drugs and, as discussed below, for human OTC drugs and animal drugs, whether or not the drugs are subject to the pre-approval provisions of the act or the PHS Act, is consistent with the statutory requirements of section 510(j)(1)(A), 510(j)(1)(B)(i), and 510(j)(1)(B)(ii) of the act. Section 510(j)(1)(A) of the act requires, among other things, the submission of a copy of

all labeling for drugs subject to section 505 or 512 of the act. Section 510(j)(1)(B)(i) requires, among other things, the submission of a copy of all labeling for prescription drugs not subject to section 505 or 512 of the act, and section 510(j)(1)(B)(ii) requires, among other things, the submission of the label, package insert, and representative sampling of any other labeling for OTC drugs not subject to section 505 or 512 of the act. We also have the authority to require that labeling be submitted in this format under other sections of the act (e.g., sections 201, 301, 501, 502, 503, 505, 506, 506A, 506B, 506C, 513-516, 518-520, 701, 704, 721, 801 of the act) and the PHS Act.

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

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

- Human OTC drugs that manufacturers regard as not subject to section 505 of the act or section 351 of the PHS Act. The manufacturer would submit a copy of the current label, the content of labeling, the package insert (if any), and a representative sampling of any other labeling for each human OTC drug that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act (proposed § 207.49(g)(2)(ii)).

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The term "label" means the container label as defined at section 201(k) of the act.

**Deleted:** The package insert for a human OTC drug is the detailed labeling included in the OTC drug package. The package insert is comparable to the labeling for prescription drugs for which we use the term "prescription drug labeling" in this proposal. We use the term "package insert" here to distinguish OTC labeling and because that term is used in section 510(j)(1)(B)(ii) of the act.

"Content of labeling" is defined at proposed § 207.1 (as discussed in section IV.A.5 of this document) and for OTC drugs refers to the content of the drug facts labeling as specified at § 201.66. Most OTC drugs do not have a package insert. However, for those that do, it is currently required to be submitted for drug listing under section 510(j)(1)(A) and (B)(ii) of the act and current § 207.25(b)(4) and (5). We are proposing to retain that requirement in proposed § 207.49(g)(2)(i) and (ii). For OTC drugs marketed pursuant to an approved application, any package insert would be included within the requirement to submit "all current labeling." The term "representative sampling of any other labeling," as used in proposed § 207.49(g)(2)(ii) and, as discussed below, in proposed § 207.49(g)(3)(ii), is defined in proposed § 207.1 and discussed in section IV.A.5 of this document. Examples of OTC drugs that a manufacturer may regard as not subject to section 505 of the act or section 351 of the PHS Act would include human OTC drugs marketed under an OTC monograph and deemed generally recognized as safe and effective (see part 330 (21 CFR part 330)).

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

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

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

- A representative sampling of advertisements for human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act. Proposed § 207.49(h)(1) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.25(b)(4). The term “representative sampling of advertisements” is defined in proposed § 207.1 and discussed in section IV.A.5 of this document.
- If we request it, for good cause, a copy of all advertisements for human prescription drugs that the manufacturer regards as not subject to section 505 of the act or section 351 of the PHS Act, including those advertisements described in § 202.1(l)(1), would be required to be submitted to FDA within 30 calendar days after our request. Proposed § 207.49(h)(2) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.31(a)(1). Section 510(j)(1)(B)(i) of the act requires, among other things, the submission of a representative sampling of advertisements and, upon request for good cause, a copy of all advertisements for prescription drugs not subject to section 505 of the act. Current § 207.31(a)(1) requires, upon request, the submission of a copy of all advertisements for prescription drugs that the manufacturer regards as not subject to section 505 of the act.

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

if needed, to contact the private label distributor. The information for a private label distributor is currently submitted on Form FDA 2658.

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

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

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

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

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

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

- Human prescription drugs. If the repacker or relabeler makes any change in the labeling of the drug repacked or relabeled, the repacker or relabeler would submit a copy of all changed labeling for each human prescription drug that is repacked or relabeled (proposed § 207.53(d)(1)). We would already have, as required under proposed § 207.49(g), the labeling for the drug provided by the manufacturer during listing, and the repacker or relabeler would not

need to resubmit it to us unless they make changes to the labeling. Proposed § 207.53(d)(1) is consistent with section 510(j)(1)(A) and (j)(1)(B)(i) of the act and current § 207.25(b)(2) and (b)(4), except that repackers and relabelers would not need to resubmit labeling when no changes have been made.

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

- Human OTC drugs that manufacturers regard as not subject to section 505 of the act or section 351 of the PHS Act. The repacker or relabeler would submit a copy of the current label, a copy of ~~any changes made to the package insert, if there is one,~~ and a representative sampling of any other labeling for each human OTC drug that the manufacturer of the drug regards as not subject to section 505 of the act or section 351 of the PHS Act (proposed § 207.53(d)(2)(ii)). The term "representative sampling of any other labeling," as used in proposed § 207.53(d)(2)(ii) and, as discussed below, in § 207.53(d)(3), is defined in proposed § 207.1 and discussed in

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section IV.A.5 of this document. Examples of OTC drugs that a manufacturer may regard as not subject to section 505 of the act or section 351 of the PHS Act would include human OTC drugs marketed under an OTC monograph and deemed generally recognized as safe and effective (see part 330). Proposed § 207.53(d)(2)(ii) is consistent with section 510(j)(1)(B)(ii) of the act and current § 207.25(b)(5), except redundant information would not be submitted.

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

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

- A representative sampling of advertisements for human prescription drugs that the repacker or relabeler regards as not subject to section 505 of the act or section 351 of the PHS Act. Proposed § 207.53(e)(1) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.25(b)(4).

- If we request it, for good cause, a copy of all advertisements for human prescription drugs that the repacker or relabeler regards as not subject to section 505 of the act or section 351 of the PHS Act, including those advertisements described in § 202.1(l)(1), would be required within 30 calendar days after our request. Proposed § 207.53(e)(2) is consistent with section 510(j)(1)(B)(i) of the act and current § 207.31(a)(1).

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

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

Drug product salvagers who do not otherwise repack or relabel the drugs they salvage would be required to provide all of the following listing information to us for each drug they list, including a drug salvaged for a private label distributor. Drug product salvagers who also repack and relabel the drugs they salvage must list those drugs as a repacker or relabeler in accordance with § 207.53.

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

drug would enable us to incorporate by reference information about the drug submitted by the manufacturer, repacker, or relabeler to obtain an NDC number under proposed § 207.33(c) and (d), as well as information submitted by the manufacturer, repacker, or relabeler to list the drug.

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

c. Registration number of each establishment. The registration number of each establishment where the drug product salvager salvages the drug would enable us to connect the salvaging activity to a particular drug and identify the specific location where the drug product salvaging is performed for the drug. This information would also be used in conducting our establishment inspections and for collecting postmarketing surveillance samples. Current § 207.25(b)(7) requires, for each drug listed, the submission of the registration number of each drug establishment at which the drug is manufactured or processed (within the meaning of current § 207.3(a)(8)), and current § 207.25(b)(3) requires the submission of the license number

of the manufacturer of drugs subject to section 351 of the PHS Act. The establishment registration number is currently submitted on Form FDA 2657.

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

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

#### 7. What Additional Drug Listing Information May Be Required?

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

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

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

We are considering this requirement because it would provide us with important data regarding a product's volume in the U.S. marketplace to assess the potential impact the product has on the public health, which, in turn, will enable us to use our limited resources more efficiently, particularly with regard to inspectional oversight. For example, we currently use data collected as a surrogate for production volume, among many other factors, in our risk-based

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

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

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

Currently, manufacturers, repackers, and relabelers must enter new or revised listing information on Form FDA 2657 (Form FDA 2658 is used when manufacturers, repackers, and relabelers enter new or revised information for a private label distributor's drug) and return the form to FDA. Under the proposal, manufacturers, repackers, relabelers, and drug product salvagers would access our electronic drug registration and listing system and review their current listing information online, making any changes where needed. Updating listing information would be less time consuming under the proposal because the manufacturer, repacker, relabeler, and drug product salvager would be able to easily access their information at

any time, and only changes to the information already in the system would need to be entered in the fields provided.

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

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

Under proposed § 207.57(b), manufacturers, repackers, relabelers, and drug product salvagers would review and update their listing information each June and December of every year. Proposed § 207.57(b) is consistent with the timeframes set forth in section 510(j)(2) of the act, which requires, among other things, that each person who registers must report certain listing information "once during the month of June of each year and once during the month of

December of each year." Under current § 207.21(b), an update of listing information must occur each June and December.

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

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

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

We recognize that because of their business practices, drug product salvagers may discontinue commercial distribution of a listed drug almost immediately after they salvage the drug. Drug product salvagers may salvage a drug, put the drug into commercial distribution by selling it to a retailer or other party, and then discontinue salvaging the drug. In that case, we intend to minimize the reporting burden on drug product salvagers by allowing the drug product salvager to provide notice of discontinuation of the drug at the same time the drug product

salvager lists the drug. We would not expect under proposed § 207.57(b)(2) that the drug product salvager inform us again, during the review and update of listing information in either June or December of the year, that the salvaged drug is discontinued. Under this proposal, we expect that our electronic drug registration and listing system would provide the opportunity for drug product salvagers to first list a drug, as required by proposed § 207.54, and then indicate that they are discontinuing the drug, as required by proposed § 207.57(b)(2). Because the drug product salvager would have provided the lot number and expiration date for the drug under proposed § 207.54(b)(2), we would not require that same information be submitted again under proposed § 207.57(b)(2).

- The date that the manufacture, repackaging, or relabeling for commercial distribution of a previously discontinued drug has resumed and any other listing information not previously required or submitted for the drug would be provided (proposed § 207.57(b)(3)). This proposed provision is consistent with section 510(j)(2)(C) of the act, which requires, among other things, that if a registrant has resumed the manufacture, preparation, propagation, compounding, or processing of a discontinued drug for commercial distribution, the registrant must provide notice and the date of such resumption, the established name and proprietary name of the drug, and other listing information required under section 510(j)(1) of the act not previously provided. The established name and proprietary name would have previously been submitted at the time of listing. Because we would be able to reference that information in our listing database, manufacturers, repackers, and relabelers would not need to resubmit the established name and proprietary name. Current § 207.30(a)(3) requires, in addition to the date of resumption of commercial distribution, that the NDC number, the established name and proprietary name, and any other listing information not previously submitted must be provided. Under the proposal,

this information would not need to be provided at this time because we would have access to it from the listing database.

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

- The June and December review and update of listing information would include the submission of all material changes in any information previously submitted under § 207.49, § 207.53, § 207.54, § 207.55, or § 207.57 (proposed § 207.57(b)(4)). Current § 207.30(a)(4) requires that any material change in any information previously submitted must be reported every June and December or, at the discretion of the registrant, when the change occurs. Material changes are listed in the definition of "any material change" in current § 207.3(a)(3). As discussed in section IV.A.5 of this document, we are proposing to broaden this definition to mean any change in any listing information provided under proposed §§ 207.49, 207.53, 207.54, 207.55, and 207.57 (except for labeling changes in arrangement or printing or of an editorial nature, or the inclusion of a bar code or NDC number on the label). Under the proposed

definition of "material change," the number of changes in listing information that are considered "material" would include more than the five types of changes considered "material" in the current definition. We are proposing a broader definition of material change because, for the reasons explained in section IV.D of this document, the accuracy of all listing information is essential for us to maintain a reliable and current drug listing database. Proposed § 207.57(b)(4) is consistent with section 510(j)(2)(D) of the act, which requires that each person who registers shall report once during the month of June of each year and once during the month of December of each year any material change in any information previously submitted pursuant to section 510(j)(1) or section 510(j)(2) of the act. Section 510 of the act does not define "material change."

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

FDA is proposing this certification to ensure that manufacturers, repackers, relabelers, and drug product salvagers have reviewed their listing information and have determined that there have been no changes. There have been many instances where manufacturers, repackers, and relabelers have not updated their listing information on a regular basis. It has been difficult for us to determine whether failure to update listing information is the result of no changes in information or noncompliance. The proposed requirement is intended to reduce these instances and improve the accuracy of our drug listing database. Furthermore, under section 301(p) of the

act, it is a prohibited act to fail to submit drug listing information under section 510(j) of the act. Failure to submit drug listing information would also render a drug misbranded under section 502(o) of the act. In addition, the proposed requirement to certify is supported by the statutory provision in section 701(a) of the act (21 U.S.C. 371(a)) that the Secretary has the authority to promulgate regulations for the efficient enforcement of the act.

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

Current § 207.30(a) provides that the updates to listing information must be submitted during each June and December or, at the discretion of the registrant, when the change occurs. Although proposed § 207.57(b) would require that listing information be reviewed and updated only every June and December, we are requesting that manufacturers, repackers, relabelers, and drug product salvagers provide all updates to listing information within 30 calendar days of a change. We are requesting that this information be provided on an expedited basis because our listing database will be more accurate if listing information is submitted sooner.

#### E. Electronic Format

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

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

- Establishment registration information required in proposed §§ 207.25 and 207.29 (proposed § 207.61(a)(1)(i));
- Information required for an NDC number in proposed § 207.33 (proposed § 207.61(a)(1)(ii)); and

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

Proposed § 207.61(a)(2) would require that the content of labeling defined in proposed § 207.1 and required under proposed § 207.49(g)(1) through (g)(3) be provided to us in electronic format. The NDC number would also be provided with<sup>9</sup> the content of labeling for each drug. As explained in section IV.E.7 of this document, the submission of the content of labeling would be made in accordance with 21 CFR part 11, except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30. As explained in section IV.E.4 of this document and stated in proposed § 207.49(g), the labeling, including the content of labeling, would not be required if the approved U.S. application number is provided by the manufacturer when the drug is listed.

In addition to the electronic submission of information under proposed § 207.61(a)(1)(i), (a)(1)(ii), (a)(1)(iii), and (a)(2)), advertisements and labeling (other than the content of labeling) required under §§ 207.49(g) and (h) and 207.53(d) and (e) would be provided to us in either paper or electronic format (proposed § 207.61(a)(3)). The NDC number would also be provided with<sup>10</sup> the advertisements and labeling. As explained in section IV.E.7 of this document, the electronic submission of advertisements and labeling, other than the content of labeling, would

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

be made in accordance with part 11 (21 CFR part 11), except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30.

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

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

- We would receive a greater quantity of accurate information in less time than it takes to receive information from paper submissions. The information received would also be more accurate because our electronic drug registration and listing system would eliminate errors associated with inputting paper-based data into an electronic system.
- The electronic transmission of the information would be easier and more efficient for both industry and us than the current use of paper forms. For example, you would receive on-screen feedback if the information submitted was not complete, reducing errors and the time and cost of communicating with us. Similarly, electronic transmission of the information would reduce significantly the time and cost associated with our processing paper forms and communicating with industry concerning errors on those forms.
- Information search and retrieval time would be reduced, allowing quicker access to the information in the database.

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<sup>10</sup> See footnote 9.

The requirement to provide listing information to us electronically is consistent with the requirement to list in section 510(j)(1) of the act: "Every person who registers with the Secretary \* \* \* shall \* \* \* file with the Secretary a list of all drugs \* \* \* . Such list shall be prepared in such form and manner as the Secretary may prescribe \* \* \* ." The requirement to provide registration information to us electronically is consistent with section 510(p) of the act: "Registrations \* \* \* (including the submission of updated information) shall be submitted to the Secretary by electronic means, upon a finding by the Secretary that the electronic receipt of such registrations is feasible \* \* \* ." Persons who register are also required to list drugs which are being manufactured, prepared, propagated, compounded, or processed for commercial distribution (21 U.S.C. 510(j)(1)).

## 2. What Was the Electronic Submission Pilot Project?

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

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

Industry representatives accessed the pilot test through our extranet to perform the following functions: (1) Initial company setup and establishment registration; (2) registration of additional establishments; (3) drug listing; (4) updates; and (5) system access, logoff, and exit. The pilot test included installation, setup, and operational testing of our electronic drug registration and listing system.

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

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

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

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

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

Electronic format submissions of registration and listing information, as well as information required for an NDC number, would consist of the electronic transmission via the Internet of the required information from manufacturers, repackers, relabelers, and drug product salvagers into our electronic drug registration and listing system.

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

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

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

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

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

- You could sign onto the system by entering the account number, user name, and password obtained by following the procedures in the guidance we intend to issue on our electronic drug registration and listing system, as discussed in section IV.E.6 of this document.
- You would then be prompted to provide general information about your company and then specific information about each establishment and drug as required in proposed part 207.
- When all of the required information is provided, your official contact would receive confirmation electronically that the information has been received by us.
- If you provide information to obtain an NDC number, the number could be issued electronically.

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

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

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

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

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

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

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

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

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

The proposed requirement to provide the content of labeling electronically is consistent with (among other things) that part of the listing requirement in section 510(j)(1) of the act which states that "Such list shall be prepared in such form and manner as the Secretary may prescribe." The proposed requirement to submit the content of labeling for human prescription drugs, human OTC drugs, and animal drugs is consistent with the statutory requirements of section 510(j)(1)(A), (j)(1)(B)(i), and (j)(1)(B)(ii) of the act. Section 510(j)(1)(A) of the act requires, among other things, the submission of a copy of all labeling for drugs subject to sections 505 or 512 of the act. Section 510(j)(1)(B)(i) requires, among other things, the submission of a copy of all labeling for prescription drugs not subject to section 505 or 512 of the act. Section

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

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

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

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

- The use of computer technology to identify changes in different versions of the labeling would greatly enhance our accuracy and efficiency in updating our listing database.
- Our ability to protect the public health would be enhanced because electronic review and comparison of labeling files would provide a higher degree of certainty that all portions of the labeling are consistent and up to date.

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

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

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

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

We would require, under proposed 207.61(a)(4), that the information in electronic format be submitted in a form we can process, review, and archive. We are prepared at this time to receive the content of labeling as a portable document format (PDF) file that is searchable. Using commercially available software, an electronic source document created by any number of programs (for example, word processors and desktop publishing programs) can be converted to a

PDF file, preserving the fonts, formatting, and graphics of the source document, regardless of the application and platform used to create it. The PDF file can be copied onto a disk or CD-ROM and shared with other users who can use PDF reading software to view, navigate through, and print the document, as well as view, search, and print the file, and copy text, tables, and figures from the file.

However, to be responsive to technological advances, we may recommend in the future that new file formats such as extensive markup language and software applications be used to submit labeling electronically. The language in proposed § 207.61(a)(4), that electronic format submissions must be in a form that we can process, review, and archive, will provide us with the flexibility to recommend file formats or software other than PDF, if appropriate, such as SPL (described earlier in sections III.B and IV.C.2 of this document). We will provide advance notice, in accordance with FDA's good guidance practice regulations under § 10.115 (21 CFR 10.115), so that affected parties will have adequate time to convert to any new format or software. In addition, we expect that such format or software will be widely available before we switch to a new technology. Changes in format and/or software will be identified in public docket number 92S-0251.<sup>11</sup> During any such transition, we will accept submissions using either file format or software.

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

Under proposed § 207.61(a)(3), advertisements and labeling, other than the content of labeling, required under proposed §§ 207.49(g) and (h) and 207.53(d) and (e) would be provided to us in paper or electronic format. Information on how and where to send labeling and advertisements that are not provided electronically will be described in the guidance document

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<sup>11</sup> This docket may be accessed on the Internet at <http://www.fda.gov/ohrms/dockets>.

we intend to develop, as discussed in section IV.E.6 of this document. Although we are proposing to require that only registration and listing information, information submitted to receive an NDC number, and the content of labeling need be submitted in electronic format, we expect to identify in public docket number 92S-0251 copies and samples of labeling and advertisements as types of documents we accept in electronic format. Under the proposal, you would have the option of submitting advertisements and labeling either electronically or in paper.

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

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

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

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**Deleted:** We do not expect to publish a draft guidance prior to publication of a final rule because we believe that the information we will need to develop our Web-based data collection system will not be conclusive until the rule is ready to be finalized.

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

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

Under proposed § 207.61(a)(1), the submission of registration and listing information (except for the content of labeling and advertisements and labeling) and the information required to receive an NDC number would be made in accordance with part 11, except for the requirements under § 11.10(b), (c), and (e) and the corresponding requirements under § 11.30. Under proposed § 207.61(a)(2) and (a)(3), the submission of the content of labeling, and advertisements and other labeling in electronic format, would be made in accordance with part 11, except for the requirements under § 11.10(a), (c) through (h), and (k), and the corresponding requirements under § 11.30. In the FEDERAL REGISTER of March 20, 1997 (62 FR 13430), we published regulations on electronic records and electronic signatures (part 11). Part 11 regulations, among other things, set forth the criteria under which records submitted to us may be submitted in electronic format in lieu of paper records. Section 11.2(b) states that, for records submitted to us, persons may use electronic records in lieu of paper records, in whole or part, provided the requirements of part 11 are met and the documents or parts of documents to be submitted have been identified by us in public docket number 92S-0251 as being the type of submission we are prepared to accept in electronic format.

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

We recently announced in the FEDERAL REGISTER our current thinking on part 11. In the FEDERAL REGISTER of September 5, 2003 (68 FR 52779), we announced the availability of a guidance for industry entitled "Part 11, Electronic Records; Electronic Signatures--Scope and Application" (the part 11 guidance). The part 11 guidance explains our current thinking regarding the requirements and application of part 11 and states that we intend to exercise enforcement discretion in the manner specified in the guidance with respect to the validation (§ 11.10 (a)), audit trail (§§ 11.10(e) and (k)(2)), record retention (§ 11.10(c)), and copies of records (§ 11.10(b)) requirements of part 11, and any corresponding requirements in § 11.30. In addition, we announced that we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of the part 11 guidance. Although we explain the relationship between the part 11 guidance and this proposal, as discussed below, you should refer to the guidance we intend to issue on electronic registration and listing for information on complying with part 11 when providing registration and listing information electronically. The part 11 requirements from which we propose exemptions in this proposal differ from the part 11 requirements for which we intend to exercise enforcement discretion, as described in the part 11 guidance. They differ because the proposed exemptions in this rule are

specific to the electronic submission of registration and listing information, including information that must be submitted to receive an NDC number and the content of labeling, for drugs that would be covered under proposed part 207, whereas the part 11 draft guidance applies to the maintenance of all electronic records and to all electronic submissions subject to part 11.

With respect to the electronic submission of registration and listing information, including the information required to receive an NDC number but not including the content of labeling and advertisements and other labeling, as previously noted, we believe, as provided in proposed § 207.61(a)(1), that several of the requirements in subpart B of part 11 are not necessary to further the goals of part 11. Because we control the electronic drug registration and listing system, certain controls for systems would not apply to the submission of registration and listing information, such as:

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

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

registration and listing information, and we could generate accurate and complete copies of records.

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

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

- The corresponding controls of § 11.30.

We are proposing to exempt the submission of electronic content of labeling from certain part 11 requirements because we believe these part 11 requirements are not critical to ensure the quality of the content of labeling that would be submitted under this proposed rule and we do not think it is necessary for industry to expend resources on controls that are not necessary to further the goals of part 11. For example, validation for the system used to generate the labeling record is not necessary because the manufacturer's verification that the information in the labeling record is accurate serves the same objective. Our review of the content of labeling is based on the version of the labeling record submitted to us. Earlier versions of the record, as well as changes made to the earlier versions, are not relevant to our analysis. In addition, our registration and listing database is designed to ensure the authenticity, integrity, and confidentiality of this information. As mentioned, we would control the database, you would only be able to enter and/or revise information in your own account, and the database would contain records of the information from which we could generate accurate and complete copies. Thus, controls related to the creation, modification, and maintenance of the content of labeling are not needed.

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

guidance announces that we intend to exercise enforcement discretion with respect to that section in the manner described in the guidance.

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

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

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

#### 9. Could the Electronic Format Requirements Be Waived?

Under proposed § 207.65, manufacturers, repackers, relabelers, and drug product salvagers may request a waiver from the proposed requirement in § 207.61(a) that information be provided to us in electronic format. This proposed waiver provision is consistent with the

Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250) which amended section 510 of the act to add section 510(p) to explicitly give the Secretary discretion to require the electronic submission of registration information upon a finding that electronic receipt of such registration information is feasible, unless the Secretary grants a request for a waiver because the use of electronic means is not reasonable for the person requesting the waiver. Under proposed § 207.65, we may grant a waiver request if the manufacturer, repacker, relabeler, or drug product salvager does not have an e-mail address and access to a computer and an ISP that can access our Web-based registration and listing database and communicate with us. The request must include a telephone number and/or mailing address where we can contact the person making the request. We intend to provide the mailing address for submitting a waiver request in the draft guidance and technical specifications on the electronic submission of registration and listing information.

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

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

paper form for submitting the required registration and listing information (including the information required to obtain an NDC number).

F. Miscellaneous

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

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

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

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

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

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

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

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

Currently, the provisions concerning a United States agent, as well as other requirements for foreign manufacturers, foreign repackers, foreign relabelers, or foreign drug product salvagers, are set forth under § 207.40. In addition, current § 207.3(a)(11) defines United States agent as a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. The definition states that "United States agent" excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present. We are proposing to revoke current

§§ 207.3(a)(11) and 207.40 and include these requirements (as revised), for example, under proposed §§ 207.1, 207.9, 207.13, 207.17, 207.33, 207.41, 207.61, and 207.69.

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

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

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

Under proposed § 207.77(a), registration of an establishment or listing of a drug does not denote approval of the establishment, the drug, or other drugs of the establishment, nor does it mean that a product may be legally marketed. Any representation that creates an impression of official approval or that a drug is approved or is legally marketable because of registration or listing would be misleading and would constitute misbranding under section 502 of the act. To clarify and consolidate current regulations, we are proposing to revise and move a similar provision in current § 207.39 to proposed §§ 207.77(a) and 207.37. Current § 207.39 states that

registration of a drug establishment or drug wholesaler, assignment of a registration number, or assignment of an NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of registration or possession of a registration number or NDC number is misleading and constitutes misbranding. The registration provisions in current § 207.39 would be included in proposed § 207.77(a), and the NDC number provisions in current § 207.39 would be included in proposed § 207.37. Proposed § 207.37(c) states that the NDC number must not be used to denote FDA approval of that drug. We are proposing to include in proposed § 207.77(a) that listing a drug would not denote approval of the drug and that any such representation would be misleading and constitute misbranding.

Under proposed § 207.77(b), assignment of an establishment registration number, inclusion of a drug in our database of drugs, or assignment of an NDC number does not denote approval of the establishment or the drug or any other drugs of the establishment, nor does it mean that the drug may be legally marketed. Any representation that creates an impression that a drug is approved or is legally marketable because it appears in our database of drugs, has been assigned a NDC number, or the establishment has been assigned an establishment registration number, is misleading and constitutes misbranding. Failure to comply with proposed § 207.37 also constitutes misbranding. We are proposing to add this provision to clarify that a drug's marketing approval status is determined, for example, under section 505 or 512 of the act, section 351 of the PHS Act, and parts 314, 514 (21 CFR part 514), and 601 of the regulations, and not under section 510 of the act or part 207 of the regulations.

Under proposed § 207.77(c), neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by section 201(g)(1) of the act. This provision reflects a

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

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

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

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

The proposal would revoke the introductory text of current § 207.37(a), which includes a description of the types of forms available for inspection, the addresses at which such forms can be inspected, and the addresses that requests for verification of registration numbers and requests for locations of registered establishments can be directed. We are proposing to revoke this introductory text because these forms would no longer be used under the proposed scheme. Instead, we intend to make most information that is available for public disclosure accessible via the Internet. This initiative would be consistent with the GPEA and would also help to reduce the number of Freedom of Information Act (5 U.S.C. 552) requests we receive for registration and listing information. Accordingly, we are also proposing to revoke current § 207.37(b), which sets forth the address to which requests for information about drug registration and listing can be directed. We note that persons may still submit Freedom of Information Act requests to the agency for drug registration and listing information that is not available on the Internet.

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

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

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

We are proposing to exempt proposed §§ 207.33(d)(1)(ii) and 207.54(b)(1) from proposed § 207.81(a) because this information may disclose a business relationship between the manufacturer, repacker, relabeler, or drug product salvager and the business from which they obtained the drug, and may constitute commercial or financial information that is exempt from public disclosure under § 20.61(c). We are proposing to exempt from public disclosure the information collected under proposed § 207.33(d)(1)(ii), which would require that repackers or relabelers, to obtain an NDC number, must provide, among other things, the NDC number assigned to the drug immediately before the drug is received by the repacker or relabeler. We also are proposing to exempt from public disclosure the information collected under proposed § 207.54(b)(1), which would require that drug product salvagers, to list a drug, must provide, among other things, the NDC number assigned to the drug immediately before the drug is received by the drug product salvager.

In addition to these changes, the proposal would make some fundamental changes to the disclosure provision in current § 207.37. We are proposing to add one category of listing

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

We are proposing, under § 207.33(c)(2)(ii), to give manufacturers the opportunity at the time of listing to identify inactive ingredients that they consider trade secret. Information identified by the applicant as trade secret would not be routinely posted on the Internet. Public disclosure of inactive ingredients not designated as trade secret at the time of listing would be authorized by the proposed regulations. We would evaluate claims of trade secret protection based on the definition of a trade secret in § 20.61(a) when making disclosure decisions in response to requests made under the Freedom of Information Act for this information and would withhold the information from public disclosure, when appropriate, under § 207.81(c). This evaluation is consistent with how FDA evaluates requests asking for inactive ingredient information that is included in approved U.S. applications. When manufacturers submit the approved application number instead of listing inactive ingredients under proposed § 207.33(c)(2)(ii), they similarly would need to identify any inactive ingredients they considered

to be trade secret. Proposed §§ 207.33(c)(2)(ii), 207.81(a), and 207.81(c) would strike a balance between manufacturers' commercial interests and the fact that it would generally be inconsistent with protection of the public health to withhold inactive ingredient information. We expect that manufacturers would only avail themselves of the opportunity to claim trade secret protection in extremely limited circumstances. We note that information in a drug's labeling, including the names of inactive ingredients, is not trade secret information.

The proposal to add information about inactive ingredients to the list of categories considered to be public information is also consistent with section 510(f) of the act. Section 510(f) of the act generally provides that listing information shall be exempt from inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health. We find that exempting, among other things, a list of inactive ingredients from public disclosure would be inconsistent with the protection of the public health. It is important for consumers to know the inactive ingredients of the drugs they might be taking because such information can be important in certain situations. For example, some inactive ingredients can trigger allergic reactions in patients. If a particular inactive ingredient appeared to trigger such reactions in an individual, and the name of the inactive ingredient was available to the public, individuals and their caregivers would be able to access such information to prevent potentially serious reactions. Additionally, some inactive ingredients may be particularly toxic to individuals with certain medical conditions and some may exacerbate a person's medical condition. If inactive ingredient information is available for drugs, individuals and their caregivers could get this information and avoid adverse reactions. We could also use inactive ingredients information to help us investigate possible drug contamination, counterfeiting, or adulteration. For example, if a drug appeared to be linked to an unexpected number of adverse

drug events or seemed less effective than expected, an analysis of the drug showing the presence of unidentified (i.e., not previously listed) inactive ingredients in that drug could suggest that the drug was adulterated or counterfeit, or that the unidentified inactive ingredient may interfere with the drug's mode of action. Additionally, the presence of an unidentified inactive ingredient in a drug product may suggest contamination or that the drug was not manufactured by the legitimate manufacturer. Generally, we believe that knowing about a drug's inactive ingredients and having such information readily available in an electronic database is consistent with protection of the public health.

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

remote possibility that the names, along with other information that may be disclosed under this proposal, could reveal a business relationship. We believe that the potential public health benefits of releasing the names of the inactive ingredients justify our decision not to exempt them from public disclosure because they outweigh the remote possibility that a business relationship could be revealed. Therefore we have concluded that the public interest in disclosure of most registration and listing information supports the proposals in the rulemaking.

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

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

Proposed § 207.81(b) would make one other conforming change to the current disclosure provision. Current § 207.37(a)(2) sets forth three categories of information that will not be available for public disclosure (except that any of the information will be available for public disclosure if it has become a matter of public knowledge or if we find that confidentiality would be inconsistent with protection of the public health). Proposed § 207.81(b) would retain the category treating as nondisclosable any information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505 or 512 of the act. As

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

#### G. Conforming Actions

##### 1. Withdrawal from Sale of Drugs with Approved Marketing Applications

We are proposing to revise our human drug regulations on applications for approval to market a new drug to make them consistent with proposed part 207. Under current § 314.81(b)(3)(iii)(a), holders of new drug applications must report to us the withdrawal from sale of a drug product. Under this provision, the information must be submitted on Form FDA 2657 within 15 working days of the drug product's withdrawal from sale. The following information must be submitted: The NDC number; the identity of the drug by established name and by proprietary name; the new drug application number or abbreviated application number;

and the date of withdrawal from sale. The reason for withdrawal of the drug from sale is requested but not required to be submitted. Section 314.81(b)(3)(iii)(b) provides the address for submitting the completed form, and § 314.81(b)(3)(iii)(c) states that reporting under § 314.81(b)(3)(iii) constitutes compliance with the requirements under current § 207.30(a) to report "at the discretion of the registrant when the change occurs."

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

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

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

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

## 2. Proposed Revisions to Other Regulations

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

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

- Section 330.1(b): As explained in section IV.C.5 of this document, the NDC number would be required to appear on OTC drug labels.
- Section 514.111(a)(12): As explained in section IV.B.2 of this document, we would refuse to approve an NADA if the drug is manufactured in an establishment that is not registered.
- Section 515.10(b)(8): The reference to "§§ 207.20 and 207.21" would be changed to "part 207" as a result of the proposed reorganization and revision of part 207.
- Section 607.3(b): Current § 607.3(b) defines "blood and blood product" to mean a drug which consists of human whole blood, plasma, or serum or any product derived from human whole blood, plasma, or serum, hereinafter referred to as "blood product." The current definition also states that "blood and blood product" also means those products that meet the definition of a device under the act and that are licensed under section 351 of the PHS Act. We are proposing to amend this definition to add the phrase "as well as licensed biologic components used in the manufacture of a licensed device." This proposed revision is intended to clarify that licensed biologic components used in the manufacture of a licensed device are covered under the definition of "blood and blood product" and that manufacturers of licensed biologic components used in the manufacture of a licensed device are required to register and list under part 607. It is important that manufacturers of licensed biologic components used in the manufacture of a licensed device register and list because licensed devices are used to ensure the safety of blood and blood products.
- Section 607.3(k): We are proposing to define "importer" as a company or individual in the United States that is the owner, consignee, or recipient of the foreign establishment's blood product that is imported into the United States.

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

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

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

Current § 607.22(a) requires the first registration of an establishment to be on Form FDA 2830 (Blood Establishment Registration and Product Listing), provides the mailing address where the Form FDA 2830 may be obtained and submitted, states that FDA will furnish a Form FDA 2830 before November 15 of each year to establishments whose registration for that year was validated under § 607.35, and states that the completed form must be mailed to us before December 31 of that year. Current § 607.22(b) states that the first and subsequent blood product listing updates shall be on Form FDA 2830.

We are proposing to reorganize and update current § 607.22 as follows: Initial and subsequent registrations and product listings by a blood product establishment for blood products would be on Form FDA 2830 (Blood Establishment Registration and Product Listing).

Manufacturers may obtain, complete, and submit the form in the following ways:

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

We are proposing these revisions to current § 607.22 to make the registration and blood product listing process for blood product establishments more efficient by utilizing the latest technology for completing and submitting registration and listing forms.

- Section 607.25(b)(1): Current § 607.25(b) lists the information required for blood product listing. Currently, blood establishments that manufacture bulk product substances and finished dosage forms must list their products under part 607 and also under part 207 to receive a

NDC number. We are proposing to revise current § 607.25(b)(1) to delete the phrase “including bulk product substances as well as finished dosage forms” because we are proposing to require these manufacturers to list only under part 207 to reduce their reporting burden. In addition, we are proposing to add the phrase “if any” after “by proprietary name” because not all of these products have a proprietary name. We are also proposing to delete the reference to Form FDA 2250 (National Drug Code Directory Input) because this form is no longer being used by CDER or CBER.

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

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

Proposed § 607.35 would state only that we will assign a permanent registration number to each blood product establishment registered in accordance with part 607.

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

National Health Related Items Code system because it is a voluntary system for medical device manufacturers that is managed by CDRH.

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

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

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

- Section 607.39: Current § 607.39 states that registration of an establishment or assignment of a registration number or assignment of a NDC number does not in any way denote

approval of the firm or its products, and that any representation that creates an impression of official approval because of registration is misleading and constitutes misbranding.

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

- Section 607.40: As discussed in section IV.A.2 of this document, we are proposing to revoke current § 207.40, establishment registration and drug listing requirements for foreign establishments, and revise and move the requirements elsewhere in proposed part 207. Consistent with the revisions to proposed part 207, we are proposing to revoke certain provisions of current § 607.40(a) and (b). We are proposing to revoke the exemption in current § 607.40(a) relating to foreign establishments whose blood products enter a foreign trade zone and are reexported from that foreign trade zone without having entered United States commerce. We are also proposing to revoke, in part, current § 607.40(b), which allows for blood, blood components, Source Plasma, or Source Leukocytes, or a component or part, under section 801(d)(4) of the act, to be imported or offered for import into the United States even if the product is not listed and manufactured, prepared, propagated, compounded, or processed at a registered foreign establishment. We are proposing to eliminate these two exemptions because

of certain statutory changes that have occurred since the publication of the final rule on foreign establishment registration and listing. Those changes include, as discussed in section IV.A.2 of this document, enactment of the Bioterrorism Act, which reflects Congress' desire to increase the nation's ability to prepare for and respond effectively to bioterrorism and other public health emergencies. Consistent with the provisions of the Bioterrorism Act, we are proposing to amend § 607.40(c) to require each foreign establishment to submit the name of each importer of the foreign establishment's blood products that is known to the establishment, and the name of each person who imports or offers for import such blood products to the United States.

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

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

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

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

- Section 1271.3: For consistency with parts 207 and 607, we are proposing to define “importer” at proposed § 1271.3(mm) to mean a company or individual in the United States that is the owner or consignee or recipient of the foreign establishment's HCT/P that is imported into the United States. For consistency with part 607, we are proposing to define “United States agent” at proposed § 1271.3(nn) to mean a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. The definition of “United States agent” would exclude mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment's agent is not physically present. The United States agent would be responsible for helping FDA communicate with you, responding to questions concerning your HCT/Ps that are imported or offered for import to the United States, and helping FDA schedule inspections.

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

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

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

In the Federal Register of January 19, 2001 (“Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing,” (66 FR 5447)), FDA announced

its intention to develop an electronic submission process for HCT/P registration and listing. The agency has developed such a system and it is currently in use on a voluntary basis.

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

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

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

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

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

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

Add § 1271.25(a)(5) to require each foreign establishment to also submit the name, the address, telephone and fax numbers, and e-mail address of each importer that is known to the establishment and the name of each person who imports or offers for import such HCT/P to the United States for purposes of importation;

Add proposed § 1271.25(a)(6) to require each foreign establishment to also submit, the name, address, telephone and fax numbers, and e-mail address of its United States agent. Under proposed § 1271.25(a)(6), each foreign establishment would have only one United States agent, and that United States agent must reside or maintain a place of business in the United States. Upon request from FDA, the United States agent must assist us in communications with the foreign establishment, respond to questions concerning the foreign establishment's products that are imported or offered for import into the United States, and assist us in scheduling inspections of the foreign establishment. If we are unable to contact the foreign establishment directly or expeditiously, we may provide information or documents to the United States agent. The foreign establishment would report to FDA changes in the United States agent's name, address, telephone and fax numbers, and e-mail address within 30 calendar days of the change.

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

- Section 1271.26: For consistency with proposed § 207.29(a), we are proposing to amend current § 1271.26 to include a change in the United States agent's name, address, telephone and fax numbers, and e-mail address. All changes in proposed § 1271.26 would be reported within 30 calendar days instead of the current requirement to report the change within 5 days.
- Section 1271.37 would be revised to delete the reference to "Form FDA 3356".

### 3. Compliance Verification Reports

On November 26, 2004 (69 FR 68831), FDA withdrew its September 2, 1993, proposal (58 FR 46587; Docket Number 92N-0291) to amend part 207 to require the completion of "compliance verification reports." These reports are printouts of information as reported to FDA

on Form FDA 2657 or Form FDA 2658. FDA had periodically mailed to domestic establishments the compliance verification report for listed prescription drugs and requested that the establishments verify or correct the information and return it to the agency within 30 calendar days. The completion of the report served to satisfy, in most cases, the drug listing updates required under current § 207.30(a). FDA provided this service to increase the accuracy of its computerized drug listing files. Because FDA is now proposing to require the electronic submission of all registration and most listing information, FDA in anticipation of this proposal has already withdrawn the September 2, 1993, proposal and has discontinued the use of the compliance verification reports. Electronic submission of registration and most listing information would make it easier for establishments to register and list. In addition, FDA's electronic registration and listing database would save registration and listing information that was submitted, thereby making it easier for establishments to access, review, and update information.

#### V. Legal Authority

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

Section 510(c) of the act requires every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug to immediately register with the

Secretary his name, place of business, and the establishment. The provisions in section 510(b) and (d) of the act require annual registration and registration of additional establishments, respectively. Section 510(i) of the act requires any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug that is imported or offered for import into the United States to register with the Secretary by providing certain information. These provisions, together with section 701(a) of the act (among others), authorize us to require the submission of the registration information specified in the proposal. The information specified in this proposal would help us identify who is manufacturing, repackaging, relabeling, or salvaging drugs and where those operations are being performed. In addition, some information (e.g., official contact information) would help us communicate with establishments more effectively and schedule inspections more efficiently.

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

facilitate recalls of products; (4) identify drugs or ingredients in short supply in the event of a national emergency; and (5) identify drugs marketed in violation of the law.

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

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

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

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

## VI. Analysis of Economic Impacts

### A. Introduction

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

Executive Order 12866 directs regulatory agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This proposed rule is not considered economically significant under Executive Order 12866.

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

Section 202(a) of the Unfunded Mandates Reform Act of 1995 (UMRA) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in expenditures by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year. Currently, such a statement is required if costs exceed about \$115 million for any one year. UMRA does not require us to prepare a statement of costs and benefits for the proposed rule because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$115 million.

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

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

Table 2.--Summary of Annual Costs and Benefits of the Proposed Rule<sup>1</sup>

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

<sup>1</sup>Based on 10-year evaluation period.

#### B. Objective

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

high quality database of drugs available on the market to enhance future uses of technology in the delivery of health care.

### C. Baseline Conditions and Scope

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

The quality and completeness of these databases depends on prompt submission of updated information from manufacturers, repackers, relabelers, drug product salvagers, and (currently) private label distributors, as well as our immediate inclusion of the data into our system. We are currently unable to verify the accuracy of the information submitted, and some manufacturers, repackers, relabelers, drug product salvagers, and private label distributors are not prompt in informing us of changes. For example, some changes in processing or packaging

might be submitted periodically rather than when such changes actually occur. In addition, forms may be mishandled, or even lost, which further reduces confidence in the databases.

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

Table 2a.--Count of Potentially Affected Healthcare Entities

Type of Entity	Establishments	Source	Additional Comment
Pharmaceutical manufacturers (human)	666	Orange Book, 2003	Includes only those pharmaceutical firms that have at least one currently marketed product in the United States. Might be an overestimate due to the possibility of applicant name duplication in the database. Does not include firms that only manufacture unapproved drug products.
Pharmaceutical manufacturers (animal)	80	Census, 2004	Includes firms that own establishments that manufacture animal drugs. Includes some firms that manufacture both human and animal drugs, so overstates the number that manufacture animal drugs exclusively. Does not include firms that only manufacture unapproved drug products.

Table 2a.--Count of Potentially Affected Healthcare Entities

Type of Entity	Establishments	Source	Additional Comment
Pharmacies	67,434	Listed below	Sum of pharmacy categories (chain store headquarters offices are not counted in this total)
Chain store (headquarters office)	25	NWDA, 2000	Covers headquarters for firms ranging from CVS (4,100 stores) to companies operating over approximately 35 stores.
Chain	20,493	NACDS, 2001	National Association of Chain Drug Stores Web site ( <a href="http://www.nacds.org">http://www.nacds.org</a> )
Independent	24,500	NCPA, 2002	National Community Pharmacists Association Web site ( <a href="http://www.ncpanet.org">http://www.ncpanet.org</a> )
Mass merchant	5,910	NACDS, 2001	National Association of Chain Drug Stores Web site ( <a href="http://www.nacds.org">http://www.nacds.org</a> )
Supermarket	8,531	NACDS, 2001	National Association of Chain Drug Stores Web site ( <a href="http://www.nacds.org">http://www.nacds.org</a> )
Institutional	7,950	ERG, 2001	Profile of the Pharmaceutical Compounding Industry: Draft Final Report. Submitted to FDA, Office of Policy, Planning, and Legislation, Office of the Commissioner, August 27, 2001.
Mail order	50	ERG, 2001	Based on discussions with Winkelman (2004)
Pharmacy benefit management companies (PBMs)	76	ERG, 2001	Profile of the Prescription Drug Wholesaling Industry: Final Report, February 12, 2001. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The figure is reported by SMG Marketing Group, Inc.
Hospitals	6,116	AHA, 2002	American Hospital Association Web site ( <a href="http://www.ahadata.org">http://www.ahadata.org</a> )
Compendium companies	5	ERG, 2004	Estimate based on discussions with Winkelman (2004)
Wholesalers/distributors	6,500	ERG, 2001	Profile of the Prescription Drug Wholesaling Industry: Final Report, February 12, 2001. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The report notes that this is probably an underestimate.
Group purchasing organizations	701	ERG, 2001	See note in previous row.
State Medicare agencies	50	ERG, 2003	Allocated one per State.
Physician offices	195,655	Census, 2000	NAICS 62111 from County Business Patterns 2000, U.S. Census Bureau.
Dentist offices	116,494	Census, 2000	NAICS 62121 from County Business Patterns 2000, U.S. Census Bureau.

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

The pharmaceutical and biological products industries (as defined by the North American Industrial Classification System (NAICS)) consist of 1,218 establishments (NAICS 325412 and NAICS 325414). ERG examined the 2003 "Approved Drug Products With Therapeutic

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Equivalence Evaluations” (the “Orange Book”) to estimate the number of companies currently operating establishments that are marketing drugs. While the Orange Book covers only products approved under section 505 of the act, there is sufficient overlap between manufacturers of products listed in the Orange Book and manufacturers of other types of products (e.g., manufacturers of OTC monograph products and animal drugs) to provide a basis for estimating the industry sector affected by the proposed rule. ERG estimates that a total of 666 companies own and operate manufacturing establishments. In addition, according to U.S. Census data, there are an estimated 80 companies that manufacture animal drugs in the United States. (There is likely overlap between human and animal drug companies.) Finally, the packaging and labeling services industry (NAICS 561910) consists of 229 companies. Each of these establishments would be affected by the proposed rule.

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

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

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

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

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

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

The development of computerized systems and the ability to electronically transmit information have had a major effect on the ways NDC numbers are used. Because the NDC numbers are designed to be unique identifiers, many sectors of the industry have built systems to