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Bar Code Label Requirements for Human Drug Products and Biological Products; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 606, and 610

[Docket No. 2002N–0204]

Bar Code Label Requirement for Human Drug Products and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a new rule to require certain human drug and biological product labels to have bar codes. The bar code for human drug products and biological products (other than blood, blood components, and devices regulated by the Center for Biologics Evaluation and Research) must contain the National Drug Code (NDC) number in a linear bar code. The rule will help reduce the number of medication errors in hospitals and other health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being given to the right patient at the right time. The rule also requires the use of machine-readable information on blood and blood component container labels to help reduce medication errors.

DATES: *Effective Date*: This rule is effective on April 26, 2004.

Compliance Dates: Drug products that receive approval on or after the rule's effective date must comply with the bar code requirement within 60 days after the drug's approval date. Drug products that received approval before the final rule's effective date must comply with the bar code requirement within 2 years after the final rule's effective date. Specific information on how the rule will be implemented can be found in section II.I of this document.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy and Planning (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0587.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In the **Federal Register** of March 14, 2003 (68 FR 12500), FDA (we) published a proposed rule that would require certain human drug and biological product labels to have a linear bar code (the March 2003 proposal). The proposal would require the bar code to contain the drug's NDC number. For blood and blood components, the proposal would require the use of machine-readable information on the container label. Our intent was to help reduce the number of medication errors in hospitals and health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug, in the right dose and right route of administration, is being given to the right patient at the right

time. For blood and blood components, the machine-readable information would perform a similar function and help prevent errors such as transfusion errors.

The preamble to the March 2003 proposal described the events that led us to issue the proposal (see 68 FR 12500 through 12503), and we refer readers to that preamble if they wish to obtain details on the events, recommendations, meetings, and literature that shaped the proposed rule. In brief, medication errors are a serious public health problem, and putting bar codes on drug products is expected to significantly reduce medication errors. Medication errors can occur at several points from the time the physician prescribes the drug to a patient to the time when the patient receives the drug. For example, the physician may write a prescription for the right drug, but in the wrong dose. The pharmacist might misread the prescription and provide the wrong drug, or read the prescription correctly and dispense the wrong drug. The health care professional administering the drug might give it to the wrong patient or give it to the right patient, but at the wrong time or in the wrong dose. Although most medication errors do not result in harm to patients, medication errors can result and have resulted in serious injury or death. Medication errors also represent a significant economic cost to the United States; one article published in 2001 (Ref. 30) estimated the direct cost to be $177.4 billion, while another (Ref. 31) estimated the cost of preventable adverse drug events in hospitalized patients to be $5,857 for each adverse drug event, with the estimated annual costs for preventable adverse drug events for a 700-bed hospital to be $2.8 million.

Bar codes can help reduce or detect potential medication errors by enabling health care professionals to check whether they are giving the right drug via the right dose and right route of administration to the right patient at the right time. The bar codes would be part of a system, along with bar code scanners and computerized databases, where:

- A patient would have his or her drug regimen information entered into a computerized database.
- Each drug would have a bar code. The bar code would provide unique, identifying information about the drug that is to be dispensed to the patient.
- In hospitals, health care professionals, such as pharmacists and nurses, would use bar code scanners (also called bar code readers) to read the bar code on the drug before dispensing the drug to the patient and to read a bar coded wristband on the patient before giving the drug to the patient. In an outpatient setting, the health care professional (such as a pharmacist) could scan the bar code on the drug and compare the scanned information against the patient's electronic prescription information before giving the drug to the patient.
- The bar code scanner's information would go to the computer where it would be compared against the patient's drug regimen information to check whether the right patient is receiving the right drug (including the right dose of that drug in the right route of administration). The system could also be designed to check whether the patient is receiving the drug at the right time.
- If the identity of the health care professional administering the drug were desired, each health care professional could also have a bar code. The health care professional would scan his or her own bar code before giving the drug to the patient.

Bar codes can also complement other efforts to reduce medication errors, such as computer physician order entry (CPOE) systems (where a physician enters orders into a computer instead of writing them on paper, and the order can be checked against the patient's records for possible drug interactions, overdoses, and patient allergies) and pharmacy-based computer systems that use a bar-coded NDC number to verify that a consumer's prescription is being dispensed with the correct drug.

We (FDA) held a public meeting on July 26, 2002, to discuss a possible rule to require bar codes on human drug products, blood, and blood components (see 67 FR 41360, June 18, 2002). Nearly 400 individuals attended that public meeting, and many submitted comments to us. We then published the March 2003 proposal. The March 2003 proposal would create a new § 201.25 (21 CFR 201.25) entitled ''Bar Code Label Requirements.'' (For biological products other than blood and blood components, the bar code requirement would exist through a cross-reference at a new § 610.67 (21 CFR 610.67.) The proposal also would amend the preexisting, voluntary provision regarding ''machine-readable'' symbols on blood and blood component container labels at § 606.121(c)(13) (21 CFR 606.121(c)(13) to require the use of machine-readable information.

We received approximately 190 comments on the proposal, and almost all comments supported the rule in whole or in part. For example, one comment said that ''FDA is to be highly commended for both the proposed regulation and the process leading to it'' while another said that the rule was an ''excellent step toward reducing medication errors.'' Other comments reported favorably on their own experiences with bar codes on drugs. One comment from a hospital said that the hospital had recently begun bedside verification of medications, using bar codes, and that the bar codes were a valuable tool for reducing medication errors. A comment from a health professional noted that his health care system used bar codes to dispense patient medications and those using robots to dispense medications reduced the manual error dispensing rate by 50 percent.

A few comments, however, were skeptical about the value of bar coding drugs. For example, one comment described problems associated with installing new technology in old buildings. The comment also feared that our rule would cause hospitals to lose their accreditation if they did not adopt bar coding technology. Another comment expressed concern about the impact on nurses' workloads. The comment said bar codes on drugs could cause nurses to spend more time administering medications because of scanning errors or problems with the bar code, but concluded that ''the ultimate outcomes will be worth the investment for the manufacturers, the providers, and ultimately the patients.''

After reviewing the comments, FDA made several changes to the rule. The principal changes between the proposed and final rule are as follows:

Proposed Rule	Final Rule
Would apply to prescription drugs (except for samples) and to over-the-counter drugs commonly used in hospitals and dispensed pursuant to an order	Applies to most prescription drugs (except for samples, allergenic extracts, intrauterine contraceptive devices that are regulated as drugs, medical gases, radiopharmaceuticals, low-density polyethylene form fill and seal containers, and prescription drugs sold directly to patients) and to over-the-counter drugs commonly used in hospitals and dispensed under an order. We explain the reasons for exempting certain prescription drugs in section II.B.4 of this document.
Did not contain a general exemption provision	Contains a limited, general exemption provision. We explain the reasons for creating a general exemption provision in section II.B.4.c of this document.
Would require a linear bar code that meets Uniform Code Council standards	Requires a linear bar code that meets Uniform Code Council standards or Health Industry Business Communications Council standards. We explain the reasons for this change at section II.D.1 of this document.
Would create a 3-year implementation period	Establishes different compliance dates depending on when a drug was approved. In general, the rule is effective 60 days after date of publication in the **Federal Register**. If a drug receives approval on or after the effective date, it must comply with the bar code requirement within 60 days of the drug's approval date. If the drug received approval before the rule's effective date, it must comply with the bar code requirement within 2 years of the final rule's effective date. For blood and blood components, a 2 year compliance date exists. We explain the implementation of this rule at section II.I of this document.

We describe and respond to the comments in section II of this document. To make it easier to identify comments and our responses, the word ''Comment,'' in parentheses, will appear before the comment's description, and the word ''Response,'' in parentheses, will appear before our response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received.

II. Comments on the Proposed Rule and FDA's Responses

A. Who Is Subject to the Bar Code Requirement? (§ 201.25(a))

Under proposed § 201.25(a), manufacturers, repackers, relabelers, and private label distributors of human prescription drug products and over-the-counter (OTC) drug products regulated under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (PHS Act) would be subject to the bar code requirement unless they are exempt from the establishment registration and drug listing requirements in section 510 of the act (21 U.S.C. 360).

In the preamble to the proposed rule (68 FR 12500 at 12503), we acknowledged that some hospitals place bar codes on drugs themselves and have reduced their medication error rates significantly, but we stated that requiring manufacturers, repackers, relabelers, and private label distributors to bar code their own products should be more efficient and result in better quality bar codes because manufacturers, repackers, relabelers, and private label distributors generally have sophisticated manufacturing processes, labeling machinery, and quality control systems that hospitals cannot afford. We added that bar coding by third parties (such as hospitals) could increase the possibility of a label error through the attachment of the wrong bar code and could lead to inconsistent bar code quality; in fact, one organization that submitted a comment at our public meeting on July 26, 2002, estimated the error rate in hospital labeling to be approximately 17 percent nationwide.

We also stated that requiring manufacturers, repackers, relabelers, and private label distributors to bar code their own products and to use the same bar coding standard would result in a more uniform bar coding system that could be used regardless of a patient's or hospital's location in the United States, and that this uniformity would also make it easier for health care professionals to train themselves on bar coding procedures and technique and make it easier and less expensive for hospitals to buy bar coding equipment.

(Comment 1) One comment stated that hospital pharmacies should be subject to the bar code requirements. The comment explained that hospitals frequently compound drugs for pediatric use and that omitting such compounded drugs from the rule would leave ''infants and children without the protections that bar codes are intended to provide.''

Another comment argued that we should exempt nuclear pharmacies from the rule. The comment claimed that a bar code requirement would subject hospital personnel and employees to additional radiation (because they would have to scan the bar codes).

(Response) Section 510(g)(1) of the act states that pharmacies

> which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail

do not have to register their establishments or list their products with FDA. Thus, if a pharmacy is exempt, under section 510(g)(1) of the act, from our establishment registration and drug listing requirements, the pharmacy is not subject to the bar code requirements.

We also note that drugs compounded at pharmacies generally would not have NDC numbers. NDC numbers are assigned to drugs that are listed under section 510(j) of the act, but, as we

explained earlier, section 510(g)(1) of the act would exempt a pharmacy from the registration and listing requirements. Consequently, a compounded drug would not be listed, would not be assigned an NDC number, and would therefore lack the information required to be in the bar code.

Regarding the comment claiming that a bar code requirement would lead to greater radiation exposure for nuclear pharmacy employees, the comment did not provide any evidence or data to show that using a bar code scanner would constitute a significant or even appreciable risk or that bar code scanners would undermine or compromise any existing measures taken to protect such employees from radiation exposure. Nevertheless, as we explain in our response to comment 24 in section II.B.4.b. of this document, we have decided to exempt radiopharmaceuticals from the bar code requirement.

(Comment 2) One comment said we should exempt hospitals, institutional providers, and large clinics from the rule. The comment interpreted the rule's reference to repackers and relabelers as covering hospitals and other providers and said that hospitals and other providers would still have to repack and relabel drugs (such as intravenous solutions and mixes). The comment declared it would be ''unrealistic'' to expect hospitals and other providers to obtain NDC labeler codes and ''participate in the NDC system.''

In contrast, several comments said we should extend the rule to hospitals or expressed disappointment that the rule did not require hospitals to use bar codes. For example, one comment said the Federal Government should establish requirements so that hospitals would have to adopt technologies to use the bar codes. Another comment said that we should ''encourage,'' but not require, hospitals to use bar code technology. The comment said that most hospitals would find it difficult to adopt bar code technology due to the age of their buildings and their construction.

Another comment asked us to clarify that relabeled, repackaged, or privately labeled drugs must have their own NDC numbers. The comment said that hospitals and pharmacies must not use the same NDC number that the drug's manufacturer used.

(Response) Some comments appear to have misinterpreted the rule. Repackers, relabelers, and private label distributors that are exempt from the establishment registration and drug listing requirements in section 510 of the act (see 68 FR 12500 at 12503; see also proposed § 201.25(a)) are not subject to the bar code requirements. Hospitals, clinics, and public health agencies that ''maintain establishments in conformance with any applicable local laws regulating the practices of pharmacy or medicine and that regularly engage in dispensing prescription drugs * * * upon prescription of practitioners licensed by law to administer these drugs to patients under their professional care'' are exempt from the establishment registration requirements (see § 207.10(b) (21 CFR 207.10(b)); as a result, such hospitals, clinics, and public health agencies are also exempt from the bar code requirements.

The rule also does not require hospitals to use or adopt bar code technology. Hospitals are free to decide whether to take advantage of the bar codes on human drug and biological products. Our legal authority, in this case, extends to the products and not to hospitals. Nevertheless, we advise hospitals and other potential bar code users that we are aware of electromagnetic interference (EMI) problems associated with the use of wireless technology products, such as cell phones, local area networks (LANs), and personal digital assistants (PDAs), in the vicinity of electrically-powered medical devices. EMI problems are a particular concern in health care facilities as well as home care settings. We caution that wireless bar code scanning technologies may present similar concerns about their electromagnetic compatibility (EMC) with other hospital equipment. We encourage hospitals and other potential bar code users to consider EMC with medical devices when developing their policies and implementing a bar code scanning system. Additional information about EMC with medical devices is available at *http://www.fda.gov/cdrh/emc*.

We recommend that interested parties gather information and conduct research about wireless bar code scanners (or other scanning or reading equipment) and their EMI potential on other medical devices. We also encourage voluntary standards development organizations, such as the Association for the Advancement of Medical Instrumentation, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the American National Standards Institute (ANSI), and the International Electrotechnical Commission (IEC) to work with us toward the goal of coordinated policies, research, and standards development to ensure a base level of EMC in all health care facilities. This would include recommendations for safely deploying wireless technology in hospitals and health care facilities.

As for entities that repack or relabel drugs, if a repacker, relabeler, or private label distributor is subject to the establishment registration requirement at section 510 of the act, then that person would also be subject to the bar code requirements. We would expect that repacker, relabeler, or private label distributor to use its own NDC numbers on its products. In other words, a manufacturer, repacker, relabeler, or private label distributor must not use an NDC number that is not assigned to it. Use of another establishment's NDC number in the bar code would cause the product to be misbranded under section 502(a) of the act (21 U.S.C. 352(a)) because the drug's label would be misleading.

B. What Products Must Have a Bar Code? (§ 201.25(b))

Proposed § 201.25(b) would require bar codes on the labels of:

- All human prescription drug products, excluding samples;
- Biological products; and
- OTC drug products that are commonly used in hospitals and dispensed pursuant to an order.

We proposed to exclude prescription drug samples because most samples are given to patients at physicians' offices, and we did not believe that physicians or patients would have or be inclined to buy bar code scanners for their own use in the immediate future. We invited comment as to whether we should require bar codes on prescription drug samples and sought cost and benefit data associated with placing bar codes on such samples (see 68 FR 12500 at 12505 and 12529).

As for OTC drug products, the phrase ''commonly used in hospitals'' reflected our primary focus of helping to reduce the number of medication errors occurring in hospitals. We added the phrase, ''dispensed pursuant to an order,'' because we knew that some products that are regulated as OTC drug products, such as mouth rinses and toothpastes, are not likely to contribute to medication errors, and are not dispensed in hospitals pursuant to a physician's or health care professional's order. Thus, the phrase, ''dispensed pursuant to an order,'' was designed to capture those OTC drug products that are likely to contribute to medication errors. The preamble to the proposed rule invited comment as to whether there was a better way to describe the types of OTC drug products that should have a bar code (see 68 FR 12500 at 12506 and 12529).

The preamble to the March 2003 proposal also invited comment on whether any specific product or class of products should be exempt from the rule and the reasons for an exemption (see 68 FR 12500 at 12511 through 12512 and 12529).

1. Should Prescription Drug Samples Be Excluded From the Rule?

(Comment 3) Several comments said we should require bar codes on prescription drug samples. One comment stated that bar codes on samples would make it easier to monitor inventory or distribution to patients. Another comment said that prescription drug samples are ''commonly dispensed in numerous hospital settings,'' such as emergency departments, and that ''the very nature of treatment and medication administration (in an emergency department) presents unique challenges for which bar coding would prove instrumental.'' The comment also stated that JCAHO requires institutions to have policies and procedures in place to control drug samples and requires quick retrieval of recalled drugs, so hospitals must keep detailed records, ''often including lot and expiration date, of drug samples dispensed to patients.'' Another comment suggested that, rather than require bar codes on all prescription drug sample labels, we could simply require bar codes on the outer package because patients receive the entire package rather than a portion of a drug sample.

Other comments also wanted bar codes on prescription drug samples for reasons unrelated to medication errors. For example, one comment said that bar codes on prescription drug samples would reduce the amount of time spent tracking samples. Another comment said that bar codes could help pharmacists identify samples that patients present to them; the comment said that patients sometimes bring prescription drug samples to pharmacists because they wish to continue receiving the same drug. A third comment said clinicians might be confused if they had to follow one procedure for bar coded prescription drugs and a different procedure for nonbar coded prescription drug samples.

Conversely, several comments agreed with our decision to exclude prescription drug samples from the bar code requirement. The comments said there would be no benefit to bar coding such products, although one comment suggested that we conduct a study to see how prescription drug samples are used in institutional settings and to determine whether they should be the subject of a future rulemaking. Another comment agreed that bar coding prescription drug samples would not enhance patient safety, but said that one possible benefit would be that manufacturers could monitor disbursement of prescription drug samples.

Other comments suggested that bar codes on samples could be voluntary or noted that bar codes can fit easily on prescription drug samples because their packaging is often larger than unit-dose packaging (so that it is technologically feasible to put bar codes on prescription drug packaging) and that the Uniform Code Council (UCC) system requires bar codes on promotional products such as samples.

(Response) We decline to require bar codes on prescription drug samples. The comments did not offer any data to contradict our position that most prescription drug samples are dispensed by physicians in their offices and that physicians and patients will not be inclined to buy or use bar code scanners. We realize that bar codes could help with inventory control and help monitor distribution of samples, but those objectives have no bearing on medication errors or drug safety and are outside the scope of this rule.

Although one comment did claim that prescription drug samples are commonly dispensed in hospitals, particularly in emergency departments, we could not determine whether the comment meant to say that hospitals administer samples to patients or whether they simply provide samples to patients to take home. We also could not determine whether such practices are common in hospitals, but note that, under section 503(d) of the act (21 U.S.C. 353(d), hospitals may distribute prescription drug samples at the direction of a practitioner who is licensed to prescribe such drugs and who received such samples. (However, sections 301(t) (21 U.S.C. 331(t)) and 503(c) of the act prohibit the sale and purchase of drug samples.) If we assume that the comment pertained to distribution of samples in hospitals, then we reiterate that the physicians directing the distribution of the samples and the patients receiving such samples will not be inclined to buy or use bar code scanners. Consequently, requiring bar codes on prescription drug samples would have little benefit insofar as medication errors are concerned.

As for the possible use of bar codes in helping pharmacists identify drugs presented by patients, we note that part 206 (21 CFR part 206) requires imprinting on solid oral dosage forms. The code imprint was designed to help identify solid oral dosage forms, particularly in emergency situations, and to help consumers and health care professionals identify drugs (see 58 FR 47958, September 13, 1993; part 206). Thus, drug imprinting already exists to help emergency departments, and pharmacists can also use the imprint codes to help identify samples presented to them by patients.

As for the voluntary use of bar codes on prescription drug samples, we do not object to such use.

2. Which OTC Drug Products Must Have a Bar Code?

(Comment 4) Several comments focused on OTC drug products. One comment agreed that only OTC drug products commonly used in hospitals and dispensed pursuant to an order should be required to have bar codes. In contrast, an OTC drug firm stated that the rule's description of OTC drug products might be clear to hospitals, but was unclear to OTC drug manufacturers. The comment said that, instead of describing the OTC drug products that must have a bar code, we should list OTC drug products, categories of OTC drug products, and/or ingredients that do not require bar codes. The comment said such a list would give ''clear direction'' as to those OTC drug products that are subject to a bar code requirement.

Two other comments expressed similar views on listing OTC drugs. One comment said we should list categories of OTC drug products that would not have to have a bar code, whereas another comment said we should list the types of OTC drugs that would or should be subject to a bar code requirement.

(Response) We decline to revise the rule to describe the OTC drug products that would be subject to §§ 201.25 and 610.67 in terms of specific drugs, categories, or ingredients. The comments' suggestion that we list OTC drug products, categories, and/or ingredients would effectively force us to engage in case-by-case analyses to decide whether a particular OTC drug, category, and/or ingredient should or should not have a bar code and force us to engage in repeated rulemakings each time we wanted to modify the list. Additionally, parties that objected to listing a particular OTC drug product or class could attempt to challenge our decisions, creating an added burden on our resources. The result would be a cumbersome, time-consuming, resource-intensive, and inefficient administrative process that would detract from, rather than contribute to, efforts to improve patient safety. The original proposal's

formulation makes the distinction we are trying to draw and places the burden on manufacturers, repackers, relabelers, and private label distributors of OTC drug products to determine whether their products are commonly used in hospitals and dispensed under an order.

We have, however, re-worded § 201.25(a) to refer to ''over-the-counter (OTC) drug products'' and to use the shorter term of ''OTC drug products'' in the remainder of § 201.25. This change corrects an oversight in the proposed rule because it referred to ''OTC drug products'' without explaining what ''OTC'' meant.

(Comment 5) Proposed § 201.25(b) had explained that an OTC drug is ''commonly used in hospitals'' if it is ''packaged for institutional use, labeled for institutional use, or marketed, promoted, or sold to hospitals.'' One comment stated that the rule's reference to OTC drug products packaged and labeled for ''institutional'' use was confusing because the rule also referred to ''hospitals.'' Thus, the comment said we should clearly define the sites to which bar coded products must be distributed and define ''hospital'' and ''institution.''

Two other comments suggested that we interpret ''commonly used in hospitals'' as ''packaged for hospital use, labeled for hospital use, or marketed, promoted, or sold to hospitals.'' Another comment said the interpretation of the phrase, ''commonly used in hospitals,'' should depend on a combination of two or more ''indicators,'' such as ''packaging designed for institutional use, package labeling for institutional use, or marketing or promotion (including through sales catalogues) to hospitals.'' The comment explained that our rule would ''inadvertently sweep a far larger range of OTC medicines into the rule's coverage.'' It also asked us to clarify that an OTC drug manufacturer would not be responsible for bar coding the drug if it was ''marketed, promoted, or sold to hospitals'' by someone else.

(Response) The proposed rule referred to ''institutional use'' because we knew that some OTC drug packages and labels state that the drug is ''for institutional use'' or ''for institutional use only'' (see 68 FR 12500 at 12505). We did not intend to imply that the rule would cover OTC drug products that were commonly used in ''institutions'' other than hospitals, and we have revised § 201.25(b) to replace ''institutional use'' with ''hospital use.'' However, we also have added the parenthetical phrase, ''or uses similar terms'' after ''labeled for hospital use'' to indicate that persons subject to the rule should adopt a common sense interpretation of § 201.25(b). For example, a manufacturer who labels an OTC drug ''for institutional use only'' and sells that OTC drug to hospitals should comply with the bar code requirement notwithstanding the fact that it labeled the drug ''for institutional use only'' instead of ''for hospital use only.'' In other words, we do not consider the OTC drug label's use of the word ''institution'' or its avoidance of the word ''hospital'' as being the determining factor in whether an OTC drug must comply with the bar code requirement.

As for defining what constitutes a ''hospital,'' the preamble to the proposed rule interpreted the word ''hospital'' as ''a facility that provides medical, diagnostic, and treatment services that include physician, nursing, and other health services to inpatients and the specialized accommodation services required by inpatients'' (see 68 FR 12500 at 12517, footnote 4 of table 2). We consider this interpretation to be sufficient for the final rule, but decline to codify this interpretation in the final rule. A codified interpretation of ''hospital'' would invite arguments as to whether a particular facility purchasing OTC drug products was or was not a ''hospital,'' whether the majority of purchasing institutions were or were not ''hospitals,'' and, as a result, would likely lead to further arguments about whether a particular OTC drug product sold to such facilities was subject to the bar code requirements. Engaging in such arguments would neither enhance patient safety, nor would it be an efficient use of our resources.

We also decline to interpret ''commonly used in hospitals'' as requiring two or more ''indicators.'' If we were to make the change as suggested by the comment, fewer OTC drug products would be subject to the bar code rule despite their use in hospitals and despite their potential for causing medication errors. For example, if we interpreted the rule to apply only to those OTC drug manufacturers who directly sold their products to hospitals, then an OTC drug manufacturer could avoid the bar code requirement simply by selling the OTC drug products, complete with labeling for ''hospital use,'' to wholesalers or middlemen for resale to hospitals. Similarly, if we were to adopt the comment's suggestion to change ''packaged for institutional use'' to ''packaging designed for institutional use,'' a firm could avoid the bar code requirement by making no distinction between its packages for retail sale and its packages for hospital use, because the package is arguably not ''designed'' for institutional use.

(Comment 6) Two comments stated that the phrase, ''dispensed pursuant to an order,'' is inappropriate because some institutions do not have orders provided by physicians or because some institutions allow nurses to request OTC drugs. Another comment suggested that we refer to OTC drugs that are ''dispensed upon a prescription of a practitioner licensed by law to administer a drug;'' the comment said this language would be clearer and eliminate any confusion as to what constitutes an ''order.''

Several comments suggested that we refer to ''non-prescription drugs used therapeutically pursuant to a prescriber's order,'' although one comment used the phrase ''pursuant to a rescuer's order.'' The comments explained that the word ''therapeutically'' would exclude OTC drugs such as toothpastes and mouth rinses. Another comment suggested that the rule state that OTC drug products ''are excluded from the bar coding requirements except for those OTC therapeutic drugs that are packaged for institutional use or specifically marketed for use in an institution for therapeutic purposes.''

(Response) The word ''order,'' in § 201.25(b), is not confined to any particular manner, document, or format for requesting a drug, nor is it confined to any particular type of health care professional. The phrase ''dispensed pursuant to an order'' should be interpreted as applying to an OTC drug that is to be administered to a patient as directed by a health care professional, regardless of whether he or she is a physician, nurse, or other professional. Consequently, we decline to revise the rule to refer to a ''prescription of a practitioner licensed by law to administer a drug'' because those terms would be more restrictive and would create more, rather than less, uncertainty over the rule's applicability to OTC drug products. For example, the word, ''prescription'' could be interpreted as requiring the practitioner to write a prescription for the OTC drug product before it could be administered to the patient. In contrast, an ''order'' could be an instruction written on a patient's medical chart, and could even be entered into the chart at the same time when the OTC drug is administered. As another example, the phrase, ''practitioner licensed by law to administer a drug'' could create uncertainty or disagreement as to whether a person was a ''practitioner,'' whether he or she was ''licensed by

law,'' and whether that license included the ability to ''administer a drug.''

Similarly, we decline to revise the rule to refer to ''non-prescription drugs used therapeutically pursuant to a prescriber's order.'' There is no apparent distinction between a ''non-prescription drug'' and ''OTC drug product,'' and requiring such drugs to be used ''therapeutically'' could result in disagreements as to whether a particular use was ''therapeutic.'' For example, a person might interpret ''therapeutic'' as meaning that the OTC drug product must have curative or healing properties and distinguish such drugs from those whose purpose is prophylactic or intended to prevent disease. Another person might distinguish between OTC drug products that provide symptomatic relief and ''therapeutic'' OTC drug products by arguing that providing symptomatic relief does not address the underlying cause of a disease or condition and, therefore, is not ''therapeutic.'' We can avoid such potential arguments by not referring to ''therapeutic'' use.

We did not understand the comment that referred to a ''rescuer's order'' and did not believe the use of the word to be an appropriate substitute for an ''order.''

(Comment 7) One comment suggested that the rule cover OTC drug products that are intended to be dispensed intact and in the original container as provided by the manufacturer, for use by inpatients. The comment explained that this description would cover various OTC drug products and also cover OTC drug products that are ''comfort medications'' that nurses can request without a physician's order.

(Response) We decline to adopt the comment's suggestion. The comment's suggested definition would encompass some OTC drug products, such as mouth rinses and toothpastes, that are not likely to contribute to medication errors but are nevertheless dispensed intact and in the original container to inpatients.

(Comment 8) One comment asked us to exclude OTC drug samples from the rule. The comment noted that we had excluded prescription drug samples because prescription drug samples are usually dispensed in physicians' offices and because we did not believe that physicians or patients would be inclined to buy or use bar code scanners. The comment claimed that the same rationale applied to OTC drug samples.

(Response) We decline to amend the rule as suggested by the comment because an amendment is unnecessary. The rule requires bar codes only for OTC drugs that are ''commonly used in hospitals'' and ''dispensed pursuant to an order.'' OTC drug samples would fall outside this bar code requirement because OTC drug samples are not ''commonly used in hospitals'' and are not ''dispensed pursuant to an order.''

(Comment 9) One comment from an OTC drug manufacturer asked if the rule applied to all packages of a specific OTC drug. The comment explained that the firm uses a ''modified open stock catalogue'' that includes all retail and some hospital-specific OTC drug products and that hospitals can buy products from the catalogue. The comment asked if the rule would require the firm to put bar codes on all OTC drug products in the catalogue or whether the firm could put a bar code on one or more OTC drug products and still offer OTC drug products without bar codes in the same catalogue. The comment appeared to suggest that hospitals could then decide which version (i.e., bar coded vs. nonbar coded) to buy, and the OTC drug manufacturer would still be in compliance with the rule.

(Response) We interpret the comment as meaning that an OTC drug manufacturer may make two versions of the same OTC drug product. Both versions would use the same drug (in the same dosage form and strength); they would differ only with respect to the presence of a bar code on the product labels. Under such a scenario, we agree that the OTC drug manufacturer could, indeed, offer both the bar coded and nonbar coded versions of the OTC drug product in the same catalogue for hospital and retail sales, and we would consider the firm to be in compliance with the rule.

However, if the OTC drug manufacturer had several different versions of an OTC drug product that is commonly used in hospitals and dispensed under an order, and the OTC drug manufacturer decided to put the bar code only on one product, we might consider the OTC drug manufacturer to be in violation of the rule. To illustrate, assume that the OTC drug manufacturer makes three different dosages of a drug: A 50 milligram (mg) tablet, a 100 mg tablet, and a 200 mg tablet, and it sells all three products to hospitals. If the OTC drug manufacturer placed the bar code on the 50 mg tablet labels, but not on the 100 mg and 200 mg tablet labels, we would not consider the OTC drug manufacturer to be in compliance with the rule. In this scenario, we would expect the OTC drug manufacturer to put bar codes on the 100 mg and 200 mg versions of its product as well.

(Comment 10) One comment asked us to clarify that the phrases relating to hospital use and to institutional use pertained only to OTC drug products.

(Response) The comment understands the rule correctly. The rule applies to all prescription drug products (except for prescription drug samples, allergenic extracts, intrauterine contraceptive devices regulated as drugs, medical gases, radiopharmaceuticals, low-density polyethylene form fill and seal containers, drug products shipped by manufacturers, repackers, relabelers, and private label distributors directly to patients, and blood and blood components). We explain the reasons for excluding these drugs later in this section.

Insofar as OTC drug products are concerned, the rule applies to those OTC drugs that are commonly used in hospitals and dispensed under an order.

(Comment 11) One comment stated that we should require bar codes on Betadine. The comment did not explain why it singled out this particular OTC drug, but stated that including drugs such as Betadine would allow computerized databases to check for potential allergic reactions.

(Response) Betadine is an iodine solution and an OTC drug product that is commonly used in hospitals, but only some versions are dispensed under an order. Thus, under the final rule, only those versions that are both commonly used in hospitals and dispensed under an order would be subject to the bar code requirement.

While Betadine has the potential to cause allergic reactions, it would be impractical to revise this rule to impose a bar code requirement based on a drug's potential for allergic reactions. For example, an individual might be allergic to a color additive used in a drug; another individual might be allergic to a different drug component. Accounting for all potential allergens would require additional data to be encoded, and it may be difficult to accommodate more data on product labels.

3. Must Vaccines Have a Bar Code?

In the preamble to the March 2003 proposal, we invited comment on the risks and benefits of including vaccines in the rule (see 68 FR 12500 at 12505 and 12529). We explained that we were sensitive to possible adverse impacts on vaccine production and availability.

(Comment 12) Most comments, including comments submitted by individual vaccine manufacturers and a pharmaceutical industry trade association, said vaccines should be subject to a bar code requirement. Some

comments also stated that we should require lot number and expiration date information to be encoded for vaccines, too, because such information is needed for accurate medical records.

In contrast, several comments suggested that we consider carefully the impact of bar coding on vaccines. Although these comments did not recommend exempting vaccines from the rule, neither did they appear to fully support bar codes on vaccines. For example, one comment said that bar codes on vaccines will have minimal impact because most vaccines are administered in physicians' offices, and bar code scanners will not be readily available at those offices. Several comments, submitted by health professional societies or organizations, urged ''caution,'' stating that a bar code requirement could disrupt vaccine supplies and create a burden that exceeded the benefits of bar-coded vaccines. Another comment suggested that we create a separate regulatory process for vaccines and that we ''engage'' the vaccine industry to address data encoding issues.

(Response) Vaccines are subject to the final rule's bar code requirements by virtue of being prescription drugs. The comments did not show that the costs of bar coding vaccines exceeded the benefits, and we note that vaccine manufacturers themselves did not indicate that a bar code requirement would adversely affect vaccine production or supplies.

We decline, however, to require inclusion of lot number and expiration date information in a vaccine's bar code. As we stated in the preamble to the March 2003 proposal, the costs associated with encoding lot number and expiration date information appear to exceed the benefits (see 68 FR 12500 at 12507–12508). The comments did not provide evidence that would alter the cost-benefit analysis regarding lot number and expiration date information, so the final rule does not require such information in the bar code. Nevertheless, as we stated in the preamble to the March 2003 proposal, we will not object if firms voluntarily encode lot number and expiration date information (see 68 FR 12500 at 12508).

We also decline to establish a separate regulatory process for vaccines. We presented our concerns regarding bar codes and vaccines in a notice of a public meeting (see 67 FR 41360, June 18, 2002) and in the preamble to the March 2003 proposal (see 68 FR 12500 at 12504 and 12505). This rulemaking process, therefore, has given vaccine manufacturers and other interested parties ample notice and opportunity to participate on bar coding matters, so there is no public health need to create a separate regulatory process for vaccine bar codes.

4. What Other Types of Drugs Should Be Subject to a Bar Code Requirement?

a. Comments seeking to cover more drug products. (Comment 13) Many comments stated that we should require bar codes on all human drugs. Health care professionals and hospitals submitted most of these comments, but the comments frequently gave no rationale for covering all human drugs or argued that failure to require bar codes on all human drugs would force hospitals to repack drugs and apply bar codes themselves, thereby increasing the risk that hospitals might apply the wrong bar code.

(Response) We decline to require bar codes on all human drugs. By focusing on prescription drugs and certain OTC drug products, the rule covers those drugs that are most likely to be involved in medication errors. We also note that the rule should reduce the need for hospitals to put bar codes on drugs.

If we required bar codes on all human drugs, then some drugs (such as samples) would have bar codes even though they are used outside the hospital setting and in situations where the patient is unlikely to have access to, or be willing to buy, scanning or reading equipment to read the bar code. Other drugs, such as certain toothpastes, mouth rinses, and even homeopathic drugs (which are ''drugs'' under section 201(g) of the act (21 U.S.C. 321(g)) would also have to have bar codes even though they are not associated with medication errors. Thus, bar coding all human drugs is unnecessary and would not contribute significantly to an overall improvement in patient safety.

(Comment 14) Two comments asked us to require bar codes on investigational new drugs or asked if investigational new drugs are subject to the rule.

(Response) Investigational new drugs have not been assigned NDC numbers because the number of investigational new drugs is constantly changing, and that constant change would exhaust the number of available NDC numbers quickly.

In addition, bar codes on investigational new drugs also could result in misleading information or compromise the clinical study. For example, if the clinical trial involved placebo controls, and the placebo used the same bar code as the investigational new drug, the bar code could mislead the computerized database into believing that the patient received an active ingredient rather than a placebo. If the placebo used a different bar code compared to the investigational new drug, the different bar code would reveal the difference between the placebo and the investigational new drug and introduce bias into the clinical study. Consequently, we decline to require bar codes on investigational new drugs.

b. Comments seeking to exclude specific drug products. Although nearly all comments supported the rule, many comments sought to exempt or exclude particular products or classes of products from a bar code requirement or asked us to create a provision allowing case-by-case exemptions. In contrast, many comments, submitted mostly by hospitals and individuals, opposed any exemptions or opposed exemptions for specific products.

(Comment 15) Several comments asked us to exclude allergenic extracts from the rule. The comments argued that allergenic extracts encompass hundreds of different antigens, are sold directly to physicians, physician group practices, and clinics (or are not commonly used in hospitals) where bar code scanning equipment would not be used or where physicians and patients would have no incentive to buy bar code scanners, and that allergenic extracts do not always have NDC numbers. Another comment said that allergenic extracts are unique and tailored to each patient, so a manufacturer that had to comply with the bar code requirement would have to obtain NDC numbers for each extract, and this process would increase the likelihood of labeling errors. The comment also stated that a bar code requirement for allergenic extracts would be ''unduly burdensome'' and expensive; the comment estimated the cost of putting bar codes on allergenic extracts to be more than $120,000 for one firm alone.

(Response) We agree that allergenic extracts are used primarily in physicians' offices and that physicians and patients are not likely to buy or use bar code scanners. Consequently, we have excluded allergenic extracts from the final rule.

Because we have decided to exempt allergenic extracts, we do not find it necessary to address the comments' claims regarding burdens and costs.

(Comment 16) Some comments asked us to exempt products that are packaged together (''copackaged products''). One comment gave examples of products sold with titration packages or sold with different strengths or types in a package or carton that are used together. The comment explained that each

component could have its own NDC number, and asked what NDC number would be used for the copackaged product.

(Response) Even if two products are packaged together, and each product has its own NDC number, the copackaged product would have its own distinct NDC number. Thus, in the comment's example, the NDC number in the bar code would reflect the copackaged product and be distinct from the NDC numbers for the individual products, and so there is no reason to exclude copackaged products from the rule.

(Comment 17) Many comments asked us to exclude medical gases from the rule. The comments explained that compressed and liquid medical gases should be exempt from the rule because:

- Gas cylinders are located at a central supply point away from patients (so bar codes cannot be scanned easily);
- There is no easy way to affix a bar code at the quick-connect patient usage area that would discriminate between gas manufacturers;
- It is not technologically or financially feasible to have bar codes or to expect paramedics (who may be administering a medical gas) to use scanners;
- Cylinders and/or connectors are specific for gases;
- Cylinders are color-coded to reduce the potential for error;
- Gases, unlike other drugs, have dosages that vary per patient; and
- There are no known adverse events linked to medical gases.

Other comments asked us to exempt oxygen and medical gases for home use, stating that patients are unlikely to have bar code scanners in their homes, or that, for oxygen, the comment knew of no adverse reactions between oxygen and other drugs.

(Response) We agree that medical gases should be exempt from the bar code requirement. We do not, however, agree with all of the comments' arguments for exempting medical gases.

We are exempting medical gases from the bar code requirement because we conclude that bar codes on medical gases are not the best way to address medication errors associated with such drug products. We agree that, because medical gas cylinders are most frequently located at a central supply point away from patients, bar codes would not be scanned easily or in sufficiently close proximity to patients.

We also agree that there is no easy way to affix a bar code at the quick-connect patient usage area that would differentiate among gas manufacturers, and that the majority of medical gas cylinders are not patient-specific, but, rather, are used to administer medical gas to multiple patients. Because of these factors, which are unique to the administration of medical gases, we believe that bar codes are not the best way to address medication errors associated with medical gases.

We disagree with the arguments regarding the number of medical gas medication errors and the existence of adequate safeguards against such errors. The comments state that there have been very few medical gas medication errors. Low numbers of medication errors, alone, cannot justify an exemption. For example, if the type of medication error is serious (such as an error that results in death), then it would be difficult to justify an exemption on the grounds that a ''low'' number of deaths occur. Moreover, we have no basis to establish a threshold or baseline number of medication errors that would determine whether a particular drug had to comply with the bar code requirement. Even if we could establish such a threshold or baseline figure, that figure would be subject to challenge because health care professionals are not required to submit adverse event reports to us; in other words, the adverse event reporting system can signal the possible existence of a problem, but it cannot reliably predict the frequency with which such problems may occur.

We also disagree with the comments' claim that current provisions for the color-coding of high-pressure cylinders sufficiently protect against medication errors. At this time, color-coding of high-pressure cylinders is an industry recommendation rather than a requirement, so we cannot assume that all affected parties will choose to follow the recommendation. Additionally, injuries and deaths have resulted from administering medical gas from incorrectly colored high-pressure cylinders.

We also disagree with the comments' claim that medical gas containers have ''unique connectors and valves'' that decrease the potential for medication errors. Like color-coding, the use of unique connectors and valves is an industry recommendation and not a requirement. Our experience indicates that these connectors and valves can be and have been compromised such that incorrect gas has been administered, resulting in deaths and injuries.

Although we do not believe that bar codes are the best way to reduce medication errors in the administration of medical gases, we recognize the need for preventing such errors and have issued guidance on the matter, including a ''Draft Guidance on the Current Good Manufacturing Practice for Medical Gases'' (68 FR 24005, May 6, 2003), as well as a ''Compressed Medical Gases Guideline'' (February 1989). We intend to continue to evaluate medication errors associated with medical gases, and, as necessary, we may propose a regulation to reduce or prevent those errors.

(Comment 18) Two comments focused on contraceptives. One comment asked us to exempt oral contraceptives. The comment stated that it will be difficult to put bar codes on oral contraceptives because the tablets are contained in individual blister cells. The comment noted that oral contraceptives also have information regarding drug regimen compliance and placebos built into the package. The comment added that oral contraceptives are used outside the hospital setting.

The other comment asked us to exclude the Copper T intrauterine contraceptive and other intrauterine devices that are regulated as drugs. The comment asserted that these products are inserted into patients by physicians, are used outside hospital settings, and present no potential dosage error or administration error.

(Response) We decline to exclude oral contraceptives from the rule. Although oral contraceptives are contained in individual blister cells, those cells are usually placed in a single package with a single label, so the bar code would go on the label rather than on each individual blister cell. As for their use, we agree that oral contraceptives are used outside hospital settings, but do not believe that they are never used in hospitals.

As for the Copper T intrauterine contraceptive and other intrauterine products, we agree that such products, when used as specified, do not present medication error risks in the same manner as other prescription drug products, and we have excluded them from the rule. (These intrauterine contraceptive products are devices, but are regulated as drugs.) We also note that some hospitals may have additional procedures, such as requiring informed consent, before these intrauterine products are inserted, and those procedures may further reduce the risk of error.

(Comment 19) One comment asked us to exclude cosmetic-drug products which the comment characterized as not being subject to dosage limitations, such as anti-dandruff shampoo, deodorants, skin protectants, soaps, and sanitizers.

(Response) We decline to amend the rule as requested by the comment. Most products described by the comment would be OTC drug products and

probably would not be dispensed under an order. As a result, such products would not be subject to the bar code requirements. (It is also possible that some products, such as soaps, would be considered to be cosmetics rather than OTC drug products and would also be outside this rule.) We reiterate that only OTC drug products that are commonly used in hospitals and dispensed under an order are subject to the bar code requirements.

(Comment 20) Several comments sought an exemption for diluents. (A diluent is an agent, usually a liquid, that dilutes a substance (a drug, in this case) or makes it less potent or less irritating.) One comment claimed that diluents are not drugs, but acknowledged that some diluents do have NDC numbers. Another comment would not put bar codes on diluents that are packaged with another drug product because, the comment asserted, misidentification could occur after the diluent has been reconstituted with the other drug product. Another comment declared that bar codes on diluents should be voluntary and driven by the market rather than by regulation. Several other comments mentioned diluents or drug/diluent kits in a list of small products that, in the comments' view, warranted a waiver from the bar code requirement.

(Response) We decline to exclude diluents from the rule. Diluents are drugs under section 201(g)(1)(D) of the act if they are intended to be components of a drug. We are aware of medication errors involving diluents, so bar codes on diluents might help reduce or eliminate such errors. For example, bar codes on diluents could help prevent the following types of medication errors involving diluents:

• Use of the incorrect or improper diluent. Certain drug products are compatible with specific diluents, so using the incorrect diluent can compromise patient safety, especially if the incorrect diluent causes a precipitate to form that is not recognized when the drug is administered. Some precipitates are not recognizable by the human eye. An incorrect diluent can also be a problem if the patient has a particular medical condition (e.g., a diabetic patient receiving a diluent consisting of dextrose in water rather than normal saline). A bar code could alert a health care professional to the presence of an incorrect or improper diluent.

• Use of the incorrect amount of diluent. This can cause an incorrect final concentration of a drug, resulting in either an overdose or underdose of the prescribed drug. A bar code could verify that a diluent's amount was correct.

• Use of a diluent alone. We have reports where diluents were administered without the active ingredient. This error appears more likely to occur when the diluent and drug are removed from their package. In one case where a patient was supposed to receive an antibiotic oral suspension which was supplied as a lyophilized powder in a small bottle and milky white diluent in a larger bottle, the patient received the diluent only and not the antibiotic itself. A bar code could alert a health care professional that he or she is administering a diluent only.

• Incorrectly packaged or labeled diluents. There have been cases where a package was supposed to contain a diluent and active drug ingredient, but the product was incorrectly packaged so that it contained two vials of diluent. A bar code could alert a health care professional that the package contains only diluents.

If, as one comment indicated, a diluent does not have an NDC number, an NDC number should be obtained for that product. If a diluent is packaged with another drug, then, as we stated in our response to comment 16 of this document, the diluent, the drug, and the copackaged product would each have its own distinct bar code. Thus, if the diluent were separated from the drug in a copackaged product, the diluent would still have its own distinct bar code, and that bar code could be scanned.

(Comment 21) One comment asked that we exclude drug products that are shipped directly to patients. The comment gave an example of peritoneal dialysis solutions and said that an exclusion would be appropriate because patients would not be inclined to buy and use bar code scanners within their homes. The comment also claimed that the product it shipped is not typically used in hospitals.

(Response) We agree, in part, with the comment. If a prescription drug product is shipped directly from a manufacturer, repacker, relabeler, or private label distributor to a patient, then we will not require that product to be bar coded. We agree that patients will not have or be inclined to buy scanners for use within their homes.

However, similiar to our response to comment 9 in section II.B.2 of this document, if the same prescription drug product is marketed to hospitals, then we will expect that drug to have a bar code. In other words, to use the comment's example of a peritoneal dialysis solution, a manufacturer could produce two different versions of the same product; the version sold directly to patients would not have to have a bar code, but the version that is intended for sale to hospitals will be subject to the bar code requirement. By requiring the latter version to be bar coded, we will help prevent or reduce medication errors in the hospital.

(Comment 22) Several comments asked us to exclude nebules from the rule. (A nebule is a vial or container that holds a drug, usually in liquid form, before the drug is administered or dispensed in a device called a nebulizer.) The comments explained that we have been reluctant to approve nebules with a label due to concerns that labeling components could leach into the nebule and contaminate the drug. One comment added that, even if we were to approve a label on a nebule, it was unclear how a manufacturer could print the bar code.

Another comment asked whether the rule should apply to pharmaceuticals packaged with low-density polyethylene (LDPE) form fill and seal containers. The comment explained that placing a bar code on such products would present a drug stability issue. The comment said that if the rule applied to these products, then drug manufacturers would need additional time to comply with the rule because they would need to conduct stability tests.

(Response) The comments are correct that printing a bar code on such products could introduce volatile impurities into the drug (because the ink from the bar code could leach into the drug). We have provided guidance on LDPE container closure systems in ''Guidance for Industry on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems'' (July 2002).

However, we also know that some products may be packaged with a foil overwrap. Consequently, we are granting a limited exemption. We will not require a bar code on LDPE form fill and seal containers that are not packaged with an overwrap, due to the potential leaching and contamination problem. (We do not need to mention nebules in this limited exemption because nebules are LDPE form fill and seal containers.) If the product is packaged with an overwrap, then we will expect the bar code to be displayed on the overwrap. A bar code on the foil overwrap (the secondary protective packaging) for individual or multiple LDPE units will not be in direct contact with the drug product, and the foil overwrap will prevent the ink and other impurities from contaminating the drug.

(Comment 23) One comment asked us to exclude prescription dental drugs from the rule. The comment claimed that prescription dental drugs are not used in hospitals and are applied by dentists in their offices or prescribed for home use, so bar codes would not be helpful.

(Response) We decline to exclude prescription dental drugs from the rule. We believe that prescription dental drugs are used in hospitals, so bar codes on prescription dental drugs would help prevent medication errors.

(Comment 24) One comment said we should exempt radionuclear drugs from the rule. The comment explained that the outside containers of radiopharmaceuticals are lead ''pigs'' that encase syringes and vials and are used to ship radioactive materials. The lead pigs are recycled, so any bar codes on the pigs would have to be removable. However, the comment claimed, a removable bar code on the lead pigs would require new labeling or shrink wrapping equipment, thus leading to a significant financial burden on nuclear pharmacies. The comment added that radiopharmaceuticals have a low ''misadministration'' rate of 30–40 reportable ''events'' annually compared against more than 14 million nuclear medicine procedures in 2002. The comment also claimed that a bar code would require nuclear pharmacies to amend their Nuclear Regulatory Commission (NRC) Agreement State licenses because the licensing authority would have to approve all labeling changes.

(Response) We agree that radiopharmaceuticals prepared at nuclear pharmacies should be exempt from the bar code requirement. The comment correctly stated that radiopharmaceuticals have a low misadministration rate. According to NRC data, the number of reportable medical misadministrations of radiopharmaceuticals has been in the range of 32 to 42 out of more than 14 million administrations per year for the last 5 years. The highest number of reportable misadministrations occurred in 1998, when there were 42 reportable events; this represented the highest total since the NRC began collecting data under the Government Performance and Results Act of 1992.

Low medication error rates are not, however, sufficient to warrant an exemption from the bar code requirement. Instead, our principal reason for exempting radiopharmaceuticals is that NRC regulations pertaining to the medical use of radiation byproducts render bar codes unnecessary for patient safety. For example, NRC regulations require, in many cases, that radiopharmaceuticals be administered under a written directive that ensures verification of a patient's identity before each administration (see 10 CFR 35.40(a) through (b), and 35.41(a) through (b)). We believe that NRC regulations pertaining to the use of radiation byproducts provide sufficient safeguards in preventing medication errors involving radiopharmaceuticals, and, because of this alternative regulatory program for these products, the benefits associated with a bar code would not justify the costs.

Because we have decided to exempt radiopharmaceuticals from the bar code requirement, we do not need to address the comment's other claims regarding labeling, packaging, and financial burdens.

(Comment 25) One comment, submitted by an OTC drug manufacturer, asked us to exempt its OTC drug products due to their ''distinctive form'' and ''clear labeling.'' The comment said that medication errors for its products (such as ready-to-use enemas, suppositories, and medicated topical creams) are ''exceedingly rare.''

(Response) We decline to exclude OTC drug products that purport to have a ''distinctive form'' and ''clear labeling.'' A product's ''distinctive form'' and labeling do not preclude the possibility of drug interactions, wrong drug, wrong dose, wrong route of administration, or other types of medication errors.

We also decline to exclude OTC drug products, or even prescription drug products, from the rule even if their potential for medication errors is ''exceedingly rare'' (as the comment claimed). We have no basis to establish a threshold or baseline medication error rate that would determine whether a product should have a bar code, and even a ''low'' medication error rate could result in death or harm to patients. Furthermore, if we linked the bar code to a drug's medication error rate, the result could be that a drug might be bar coded at one time if its medication error rate exceeded the threshold, but not bar coded once the medication error rate fell below that threshold, and this could create confusion. For example, assume that the rule based the bar code requirement on a medication error rate of 5 percent. If Drug X had a medication error rate of 5.2 percent in Year A, it would be bar coded. If Drug X had a medication error rate of 4.9 percent in Year B, then it would not be bar coded. However, in all likelihood, in Year B, both bar coded and nonbar coded versions of Drug X would exist in the marketplace. If Drug X's medication error rate was 5.1 percent in Year C, the drug would, again, be subject to the bar code requirement. In such circumstances, the bar code would lose its value and reliability, insofar as medication errors are concerned, because hospitals would confront a constantly changing environment of drugs that have or lack bar codes, and hospitals would either not rely on such codes or lose confidence in the bar code system.

(Comment 26) One comment asked whether pharmacy-compounded prescription drugs would be subject to the bar code requirement.

(Response) As we noted in the response to comment 1 of this document, under section 510(g) of the act, pharmacies:

> which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of such practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail

do not have to register their establishments or list their products with FDA. Thus, a pharmacy that compounds drugs in accordance with this provision would probably fall outside § 201.25(a) and compounded drugs made by that pharmacy would not have to bear a bar code.

We also note that pharmacy-compounded drugs do not have NDC numbers.

(Comment 27) Several comments focused on drugs in small vials or containers. Comments from several drug manufacturers and a trade association suggested that we exempt small vials and/or small containers from the rule, and several of these comments mentioned 5 milliliter (mL) vials, suppositories, small ophthalmic containers, prefilled syringes, and blister packs as examples of products that need an exemption. The comments stated that some vials or containers would be too small for a bar code. One comment suggested exempting vaccine unit-of-use containers if a manufacturer demonstrated an inability to apply a bar code due to space limitations.

In contrast, several comments strongly opposed exemptions for small vials and ampules. These comments explained that many of these products are high-

risk medications or that most injectable products come in small vials or ampules. Other comments said that liquid medications are more often linked to medication errors than solid dosage forms, so creating an exemption for vials and ampules would undermine the rule's effectiveness. Other comments opposed exemptions for small vials because the absence of a bar code would force hospitals to apply bar codes to the products themselves, and this would create the potential for labeling errors by the hospital.

One comment, submitted by the UCC, stated that, ''No [UCC] pharmaceutical member has presented the UCC with a healthcare product too small for a [Reduced Space Symbology] symbol.'' However, the UCC could not preclude the possibility that some small product could not be bar coded, although it did note that one firm had put bar codes on vials as small as 1 mL. The UCC comment also contained attachments describing how several pharmaceutical manufacturers (Abbott Laboratories, Baxter Healthcare Corp., Pfizer, Inc., and Aventis Behring) had decided to put bar codes on injectable pharmaceuticals, intravenous solutions, and other drug products.

(Response) We decline to exempt small vials or containers (including suppositories, prefilled syringes, and other small products for which comments sought exemptions). We agree that the risk of medication errors for these products cannot be ignored, and we also find the UCC's comments persuasive. If several pharmaceutical companies have already shown their ability to place a bar code on a 1 mL vial, we cannot justify a blanket exemption for comparatively larger products, such as 5 mL vials, and prefilled syringes.

Furthermore, we note that § 201.25(c) requires the bar code to appear on the drug's label. For some products described by the comments, the drug's label appears on an overwrap or packaging. Alternatively, it may be possible to modify the drug's immediate container to accommodate a label bearing a bar code.

c. Comments seeking a general exemption provision. (Comment 28) In the preamble to the March 2003 proposal, we explained our reasons for not including a general exemption provision (see 68 FR 12500 at 12511 through 12512). We noted that industry-conducted pilot studies had placed reduced space symbology (RSS) bar codes on small vials and that those studies suggested that almost all products are capable of bearing a bar code. We also pointed out practical problems with an exemption provision, such as potential arguments as to whether it was ''feasible'' to affix a bar code and the resources that would be needed to deal with exemption requests (id.). Nevertheless, the preamble to the March 2003 proposal invited comment on whether we needed to create a waiver provision and how we could create a provision that would minimize the potential for misuse (see 68 FR 12500 at 12529 (question 8)).

Most comments opposed a general exemption or waiver provision. The comments said we would find ourselves expending resources to deal with exemption requests and that exemptions would cause more harm than good. Some comments opposed creating an exemption mechanism because they would prefer to have manufacturers repack their products or develop packaging that would support a bar code. Other comments noted that, if we exempt various products from the rule, hospitals will be forced to bar code those products themselves, and this could result in labeling errors and require hospitals to rely on two different data systems (one for bar codes with NDC numbers and another for drugs that the hospital has bar coded itself).

A few comments suggested that we create an exemption provision that would consider requests on a case-by-case basis or would be ''limited.'' The comments did not suggest how we might prevent misuse of an exemption provision. Another comment asked that we define an exemption review process.

(Response) Given the number of comments we received requesting an exemption for a specific product or class of products, the fact that the final rule contains certain categorical exemptions requested by some comments, and our inability to predict every future product or class of products for which an exemption might be justified, we felt it would be prudent to add a general exemption provision to the rule. Consequently, we have added a new § 201.25(d) which states that we may, on our own initiative or in response to a written request from a manufacturer, repacker, relabeler, or private label distributor, exempt a drug from the bar code requirement. The exemption request, under § 201.25(d)(1)(i), must document why compliance with the bar code requirement would adversely affect the drug's safety, effectiveness, purity, or potency or not be technologically feasible. The request must also explain why the problem cannot be reasonably remedied by measures such as package redesign or use of overwraps. Alternatively, under § 201.25(d)(1)(ii), the request must document why an alternative regulatory program or method of product use renders the bar code unnecessary for patient safety. For example, as explained earlier in our response to comment 24 of this document, we exempted radiopharmaceuticals from the bar code requirement because existing NRC regulations on the medical use of radiation byproducts render the bar code unnecessary for patient safety.

Section 201.25(d)(2) provides the address to which exemption requests should be sent. For human drug products, the request should be sent to the Office of New Drugs (HFD–020), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. For biological products, the request should be sent to the Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852.

We reiterate that we have created this general exemption provision to allow us to efficiently and justly address products or classes of products that we have not already considered. We emphasize that almost all drug products are capable of bearing, and should in fact bear, a bar code. We will not consider written requests that are based on other reasons (such as financial reasons, a claimed low rate of medication errors, or a claim that the product is somehow unique such that medication errors do not occur or rarely occur). Similarly, we will not entertain written requests seeking an exemption for a particular drug, class of drugs, or group of products when we have already refused to grant an exemption for the same drug, class of drugs, or group of products in this final rule. The general exemption provision is intended to be used in rare cases.

If we refuse to grant an exemption in response to a written request, our decision can be reviewed under our existing regulation at 21 CFR 10.75, ''Internal agency review of decisions.''

5. Should Medical Devices Be Excluded From the Rule?

The preamble to the March 2003 proposal explained that we did not intend to issue any bar code requirement for medical devices at this time (see 68 FR 12500 at 12506). The preamble to the March 2003 proposal stated that devices present different issues compared to human drug and biological products and that we would continue to study whether to develop a proposed rule to require bar codes on

medical devices to prevent or reduce medication errors (id.).

(Comment 29) Two comments said we should reject the device industry's request for further study and require bar codes on devices. The comments said that implantable devices are made to detailed specifications and sometimes fail, so one could presume that a device manufacturer would recall defective devices. The comments added that bar codes on devices would help create patient records that could be easily searched so that hospitals could determine an appropriate course of action if a patient received an implantable device that was recalled.

Other comments argued that we should examine the benefits of bar code labeling on devices or that bar codes would be helpful on certain devices. For example, one comment said that patient safety would be further enhanced by applying bar codes to devices such as blood bags, filters, and apheresis kits.

Conversely, one comment agreed with our decision to omit devices from the rule. The comment said that devices present ''unique'' issues, such as product diversity, evolving coding technology, and unique product identification needs that are often negotiated between customers and device manufacturers. The comment recommended that we allow for voluntary use of Universal Product Numbers (UPNs) on devices in either the European Article Number/Uniform Code Council (EAN/UCC) or Health Industry Business Communications Council (HIBCC) standard. The comment explained that the UPN system is established and provides greater consistency with global identification trends compared to the NDC number.

(Response) We decline to include devices in the final rule. Unlike drugs, medical devices do not have a standardized, unique identifying system comparable to the NDC number. (There is a National Health Related Items Code (NHRIC) system for identifying and numbering marketed medical device packages, but participation in the NHRIC system is voluntary, and the database may contain out-of-date information due to industry acquisitions and mergers.) The absence of a standard, numerical identification system comparable to the NDC number is one of several issues that complicate efforts to put bar codes on medical devices for purposes of preventing or reducing medication errors.

We also note that permanently implantable devices are subject to our device tracking requirements at part 821 (21 CFR part 821), and those requirements can be quite detailed. For example, under § 821.25(a)(2)(iii), a device manufacturer must have a method of tracking each device that it distributes that enables the manufacturer to give FDA, within 10 working days of a request from FDA, information regarding the name, address, telephone number, and social security number (if available) of the patient receiving the device.

As for voluntary use of UPNs on medical devices and the use of EAN.UCC or HIBCC standards, we recognize that some devices already bear a bar code for reasons relating to purchasing or inventory control, and we have not objected to their use nor to the bar code standards used.

C. What Must the Bar Code Contain? (§ 201.25(c)(1))

1. Should We Require the Bar Code to Contain the NDC Number?

Proposed § 201.25(c)(1) would require the bar code to contain, at a minimum, the drug's NDC number. The NDC number identifies each drug product that is listed under section 510 of the act or section 351 of the PHS Act.

(Comment 30) Two comments claimed that their products, allergenic extracts, do not have NDC numbers. The comments stated, as part of a request to have allergenic extracts excluded from the rule, that FDA has allowed generic groupings for allergens under one NDC number. The comments added that they market nearly 200 to 300 allergens in four different package configurations each, so, if allergenic extracts had to carry bar codes, the firms would need from 800 to 1,200 new NDC numbers respectively, and this would have ''enormous'' implications for the firms and FDA.

(Response) As we stated in our response to comment 15 in section II.B.4.b of this document, we have excluded allergenic extracts from the rule. As a result, issues regarding NDC numbers for allergenic extracts are moot.

(Comment 31) Several comments focused on the NDC number itself. One comment said that the NDC number contains the necessary information for bar code purposes. However, several comments argued that OTC drug products should be allowed to use the Universal Product Code (UPC) number either instead of or in addition to the NDC number. Some comments said that OTC drug manufacturers would incur thousands of dollars of ''unnecessary extra 'new item' costs'' because different NDC numbers would be necessary for new, minor formulation changes to their drugs and create logistical complications for retailers (because retailers use the UPC codes). Two comments said that requiring OTC drug bar codes to contain the NDC number would increase the demand on NDC numbers, increase FDA's workload, or exhaust the number of available NDC numbers. One comment said it should be feasible for a database to handle both NDC and UPC numbers, whereas another comment said that allowing OTC drug products to continue using UPC numbers would make more NDC numbers available for other drug products and thus benefit the NDC number system.

Another comment supported the use of the NDC number with four extra digits. The comment said this 15-digit number, called ''NDC Plus Four,'' would identify individual doses and vital information about the drug, including, among other things, the drug's lot number, expiration date, and recall status.

Another comment asked us to change the NDC number so that it contained a drug's expiration date.

(Response) We decline to amend the rule as suggested by the comments. The UPC code does not necessarily identify a unique drug product. For example, if an OTC drug manufacturer made and sold a particular drug product, that drug product would have a UPC code, and it would also have a unique NDC number. If the OTC drug manufacturer reformulated the product (such as changing an ingredient), the manufacturer could use the same UPC code for the reformulated product, but the reformulated drug would have a different, unique NDC number. This could be significant to a patient's health if, for example, the reformulated product contained an ingredient that caused allergic reactions or drug interactions. Thus, requiring the use of NDC numbers, rather than UPC numbers, will help ensure that the drug is identified correctly.

Additionally, as we stated in the preamble to the March 2003 proposal (see 68 FR 12500 at 12507), we intend, through a separate rulemaking, to change the NDC number so that it becomes a unique identifying number for listed drugs. If we were to allow the use of other coding systems, such as UPC numbers that did not contain the drug's NDC number or an NDC number with additional digits, persons who wanted to decipher a drug's bar code would need to consult multiple information sources, and this would increase the likelihood that some information and databases might not be updated as frequently as others, that

some information might be unavailable, or that the information would be presented in different or incompatible ways. Although we understand the OTC drug industry's reservations about changing UPC codes to include NDC numbers because of a possible cost impact, § 201.25(b) only requires bar codes on OTC drug products that are dispensed under an order and are commonly used in hospitals. Furthermore, as we stated in our response to comment 9 of this document, we will allow OTC drug manufacturers to create bar coded and nonbar coded versions of the same OTC drug product; the bar coded versions, which would be intended for hospital sale and use, would carry the NDC number in the bar code. The versions intended for retail sale could continue to use the UPC code.

We also decline to revise the NDC number to include expiration dates or to add more digits to the NDC number. Revising the NDC number is outside the scope of this rule. Furthermore, expiration dates vary with each new batch or production run, so if we were to revise the NDC number to include expiration dates, we would quickly exhaust the number of available NDC numbers and be forced either to redefine the NDC number or develop an alternative system relatively quickly, and other databases that relied on the NDC number would also be forced to adapt or develop new systems themselves. Restructuring the NDC number in this manner would, therefore, be impractical and costly.

Similarly, adding more digits to the NDC number might be disruptive for those databases that already use or rely upon the NDC number. Those databases would either have to reconfigure themselves to handle 14-digit numbers (assuming all preexisting NDC numbers were modified to contain 14 digits) or reconfigure themselves to handle 10- and 14-digit NDC numbers (assuming that preexisting NDC numbers remained the same, but new drugs would receive a 14-digit number). Such reconfigurations could be expensive for those who maintain the databases and those who use them. A 14-digit number could also be either redundant or confusing in comparison to the Global Trade Item Number (GTIN). As the preamble to the March 2003 proposal mentioned, the GTIN is a 14-digit number which, when used in a bar code on drug products, contains the NDC number in conjunction with a code that identifies the product's packing level (see 68 FR 12500 at 12506).

(Comment 32) Two comments asked us to ensure that different parties use different NDC numbers. One comment said that the proposed rule failed to explain how repackers will distinguish a repacked product from the original manufacturer's package. The comment suggested that manufacturers use certain digits to signal the presence of an original manufacturer's package and that repackers use other digits to identify repackaged products. The comment said we should require repackers to have a manufacturer's identification number.

The other comment asked that we ensure that hospitals do not use the manufacturer's NDC codes when repacking a drug.

(Response) As we stated in our response to comment 2 of this document, if a repacker, relabeler, or private label distributor is subject to the establishment registration requirement at section 510 of the act, then that person is also subject to the bar code requirements and must use its own NDC numbers on its products. In other words, a manufacturer, repacker, relabeler, or private label distributor cannot and should not use an NDC number that is not assigned to it. Use of another establishment's NDC number in the bar code would cause the product to be misbranded under section 502(a) of the act because the drug's label would be misleading.

Hospitals, though, are exempt from the establishment registration requirements. Consequently, hospitals themselves are not subject to the bar code requirement, and we consider drug repacking and dispensing operations inside hospitals to be within the practice of pharmacy.

(Comment 33) Several comments addressed possible changes to the NDC number. The preamble to the proposed rule stated that we intended to redefine the NDC number through a proposed rule on drug establishment registration and listing (see 68 FR 12500 at 12506). Most comments opposed any redefinition of the NDC number. One comment said that redefining the NDC number would create confusion, possibly harm patients (although the comment did not explain how such harm would occur), and undermine the bar code rule. Other comments said that redefining the NDC number would be costly and disruptive to various databases that rely on or use NDC numbers. One comment said that we should not make a final bar code rule effective until the drug industry has had the opportunity to understand and comment on any changes to the NDC number. A different comment said we should consult various ''stakeholders'' before we make changes to the NDC number. Another comment said that we did not need to redefine the NDC number because the GTIN would provide ''sufficient direction.''

(Response) As we stated in the preamble to the March 2003 proposal, we intend to revise our drug establishment registration and listing regulations to make the NDC number unique and more useful to informational databases, whether those databases are created to prevent medication errors, to obtain the latest information about a drug, or to track drug use and distribution. We are still preparing the proposed rule, and when we publish it in the **Federal Register**, we will invite comment on our proposed NDC number changes. Until we revise our drug establishment registration and listing regulations, the current requirements at § 207.35 continue to apply to the NDC number.

We also must point out that, even under a proposed drug establishment registration and listing rule, assuming there is no change in the product or packaging, we do not intend to replace currently-used NDC numbers. For existing NDC numbers, we would consider issuing a new number to an existing drug product only if there were two drugs that had the same NDC number.

(Comment 34) One comment criticized the NDC number, stating that it cannot tell whether the right dose is being administered because the actual dose may be a partial dose or multiple doses of the drug identified by the bar code. The comment said this reflected a technological limitation with NDC numbers, so the comment suggested that the computer systems used to document drug administration alert users and require manual intervention by health care professionals to verify doses.

(Response) The comment is correct that the NDC number may have certain limitations when different dosages are administered from a single package or when partial dosages are administered. For example, assume that a drug's package contains 20 tablets. The drug's NDC number will reflect the fact that the package contains 20 tablets. If the drug administered to the patient consists only of one tablet, then scanning the NDC number for the package alone will not show the correct dose given to the patient. The NDC number's principal value, in this scenario, is verifying that the correct drug in the correct dosage form is being administered. As another example, some drug product labels do not state pediatric dosages, so a physician might prescribe a partial dose for a pediatric patient. In this scenario, the NDC

number's principal value is verifying that the correct drug, in the correct dosage form, is being administered.

Regarding the comment's suggestions concerning computer systems, we agree that it could be helpful if a computerized database alerted health care professionals to check dosages given to patients. However, we do not intend to create, maintain, or regulate the databases that scanning equipment would consult to decode NDC numbers, so we advise parties to consider this issue when they develop computer systems associated with scanners to decode the NDC numbers.

2. Should the Bar Code Contain Lot Number and Expiration Date Information?

The March 2003 proposal would not require the bar code to contain the drug's lot number or expiration date. In the preamble to the March 2003 proposal, we explained that we were unable to show that the benefits associated with encoding lot number and expiration date information exceeded the costs, so we proposed to omit lot number and expiration date information from the bar code (see 68 FR 12500 at 12507). However, we also said that we would not object if drug manufacturers, repackers, relabelers, and private label distributors decided to encode lot number and expiration date information voluntarily (id. at 12508). We stated that industry representatives had suggested that they might add such information if a demand existed for it (id.), but we did not know whether hospitals and other health care facilities would be willing to pay more for drugs that had lot number and expiration date information encoded in the bar code. We invited comment on the costs and benefits associated with putting lot number and expiration date information in the bar code.

(Comment 35) Many comments urged us to require lot number and expiration date information in the bar code, but did not provide evidence to support their views. Instead, most comments declared that lot number and expiration date information would make it easier to identify recalled, contaminated, and expired drugs, would improve entries into medical records, or would provide greater patient safety. Other comments said we should phase-in a requirement to encode lot number and expiration date information over an extended time period, but did not discuss why a phased-in approach would alter the cost-benefit problem that we identified in the preamble to the proposed rule. Some comments would extend the rule's effective date to give firms more time to encode such information. Another comment urged firms to encode lot number and expiration date information, but only if the costs were not passed on to hospitals.

Other comments advanced different arguments for requiring lot number and expiration date information as part of a bar code. For example, one comment stated that the American Society of Hospital Pharmacists and others want lot number and expiration date information encoded, and so we should defer to them. Several comments said manufacturers should encode such information because they could do so at less cost compared to hospitals.

Several comments advocating the inclusion of lot number and expiration date information in a bar code argued that technology could encode such information. For example, one comment claimed that the information can be easily encoded using two-dimensional symbologies and noted that some manufacturers plan to encode such information voluntarily. Another comment noted that the GTIN, rather than the NDC number alone, could be used to provide additional patient safety information. Another comment declared that encoding lot number and expiration date information could be inexpensive because, the comment noted, firms already print the same information, in human-readable form, on packages.

In contrast, other comments supported our decision to omit lot number and expiration date information from the rule. Several comments conceded that the information could help trace recalled drugs and help with product inventory, but said that the information would not significantly reduce medication errors and that the costs of encoding the information would exceed the benefits. For example, one comment estimated that encoding lot number and expiration date information would cost $7,500 to $20,000 per manufacturer's line, excluding costs to verify the information. Several comments expressed concerns about the impact on production line speed. For example, one comment said that the online printing equipment that would be needed for encoding lot number and expiration date information is ''highly ineffective and unreliable'' at production speeds above 120 units per minute and that alternatives, such as preprinting labels, would present serious good manufacturing practice (GMP) concerns in verifying that the right label with the correct lot number and expiration date is used on the correct product. Another comment said that online printing and verification technology has not been demonstrated at production line speeds of 250 to 300 units per minute. A different comment listed various problems associated with online printing of lot number and expiration date information, such as adverse impacts on line speed and print quality, the need to develop unique bar codes for each packaging run, and limiting packaging options until printing and packaging technology becomes capable of supporting online product speeds and adequate print quality.

Another comment said we were correct to omit lot number and expiration date information from the rule because it would make bar coding more complex and perhaps discourage manufacturers from making unit-dose packages. The comment, along with other comments opposed to requiring lot numbers and expiration dates in a bar code, shared our view that the market would determine whether manufacturers and others encode lot number and expiration date information voluntarily.

One comment suggested that, if we decide to require lot number and expiration date information to be encoded, the information should only go on shipping cartons and not on individual packages because this would reduce the manufacturer's costs.

The comments also disagreed on how to interpret our recall data. The preamble to the proposed rule stated that we had examined the number of recalled drugs from fiscal year 1997 through fiscal year 2002 and that, while there were 1,230 recalls during that time period, there were few reports of adverse experiences associated with the administration of a recalled drug (see 68 FR 12500 at 12507). One comment said this data supported inclusion of lot number and expiration date information in the bar code because Class I recalls represent a reasonable probability that the use or exposure to the drug will cause serious adverse health consequences or death, and 97 of the 1,230 recalls were Class I recalls. In contrast, a comment that opposed inclusion of lot number and expiration date information in the bar code said the data were not sufficient to show any public health problem resulting from the administration of recalled or expired drugs.

(Response) The final rule does not require lot number or expiration date information to be included in the bar code. As we stated in the preamble to the March 2003 proposal, the data available to us do not indicate the magnitude of the public health problem associated with administering expired or recalled drugs, and we cannot

quantify the patient safety benefit associated with requiring lot number and expiration date information in the bar code (see 68 FR 12500 at 12507). The potential burden of encoding lot number and expiration date information appears to outweigh the potential benefit of encoding such information.

We emphasize that we do not dispute whether encoded lot number and expiration date information would be helpful in certain contexts that are unrelated to medication errors. We also do not dispute that the technology exists to encode such information or that certain firms have expressed their intent to encode such information. Nevertheless, while we recognize the strong desires expressed by some regarding lot number and expiration date information, we must also recognize the potential impact on manufacturers, repackers, relabelers, and private label distributors if we required them to encode lot number and expiration date information. The evidence before us indicates that the costs associated with encoding lot number and expiration date information, insofar as medication errors are concerned, exceed the benefits, so we decline to require such information as part of the bar code.

We reiterate that we will not prevent or prohibit firms from encoding lot number and expiration date information if they wish to do so, and we note that some drug manufacturers are encoding or intend to encode such information. We also remind hospitals and other potential bar code users that lot number and expiration date information may be encoded in two-dimensional or other technologies, so if they intend to purchase drug products with lot number and expiration date information encoded, they should consider carefully their scanning or reading equipment purchases (see 68 FR 12500 at 12507).

(Comment 36) Several comments would require other information to be encoded. For example, one comment said we should require the bar code to contain information regarding the drug's concentration, amount, and route of administration. The comment explained that information on the drug's concentration and amount could prevent errors involving concentration or overdose. It explained that information regarding the drug's route of administration could be helpful because, the comment claimed, some drugs are not to be administered intravenously or as major nerve anesthetics. Another comment focused on clotting factor products and wanted the bar code for these products to contain (among other things) the drug's brand name and number of units in a vial. The comment recognized that encoding the number of units in a vial might be difficult, but said that persons with hemophilia and other bleeding disorders often carry vials, but not package boxes that contained the vials, with them. It added that the additional information would provide better information about the product's efficacy, i.e., whether the patient achieved the expected hemostatic response given the units administered.

Several comments asked that we require the bar code to indicate the drug's waste disposal status under the Resource Conservation and Recovery Act (RCRA). The comments explained that medical personnel might not know that a particular drug, when it becomes a waste product, is regulated under RCRA. Some comments suggested that the drug's waste disposal status could be identified by adding another digit to the NDC number. One comment suggested that we coordinate with the Environmental Protection Agency to capture a drug's hazardous waste disposal status.

(Response) We decline to revise the rule as suggested by the comments. The NDC number, under a bar code system, is a link to information held in a database. For example, assume that the bar code contains the drug's NDC number. The scanner reading the bar code would transmit the NDC number to a computerized database, and that database could be designed to generate information regarding the drug's names, dose, concentration, route of administration, waste disposal status, etc. In other words, the information sought by the comments could be built into a database and does not have to be encoded in the bar code itself and does not require changes to the NDC number.

3. Can Information Be Omitted From the Label to Accommodate the Bar Code?

(Comment 37) Several comments suggested that we allow firms to exclude certain information from their labels so that they could affix a bar code. Some comments sought relief from the labeling requirements at § 201.10(i) (21 CFR 201.10(i)); that provision requires drug labels to contain the drug's proprietary name, established name (if one exists), an identifying lot or control number, and the manufacturer's, packer's, labeler's, or distributor's name. One comment suggested amending § 201.25(c), regarding the bar code's placement on a label, to state that any drug complying with the bar code requirement is exempt from § 201.10(i)(1)(iii) and (i)(1)(iv) (provisions regarding the identifying lot number or control number and manufacturer's, packer's, labeler's, or distributor's name) if the packaging size is such that the required information is not easily readable.

One comment sought clarification regarding a label requirement imposed by another Federal agency. The comment claimed that the Consumer Product Safety Commission (CPSC) has a regulation that requires drug products labeled for hospital use only to also bear a statement regarding use in households without young children.

Several comments focused on small labels. One comment stated that excluding ''some'' label information would help print high quality bar codes; the comment identified the manufacturer's or distributor's name and address as information that it would exclude from a label. Similarly, another comment would remove the manufacturer's name from the label because, the comment explained, the manufacturer's name is on the outer package and is part of the NDC number. Another comment stated that the only way to create room for a bar code on a small label would be to reduce font size, but the resulting print would be difficult to read.

(Response) We decline to amend the rule as suggested by the comments. In most cases, the information that the comments would remove from the label is required by Federal law, so we are unable to provide the relief sought by the comments. For example, section 502(b)(1) of the act considers a drug to be misbranded if it is in package form and its label does not contain ''the name and place of business of the manufacturer, packer, or distributor.'' Section 502(b) of the act does not authorize any exemptions from this requirement, so we cannot delete such information from the label simply to accommodate a bar code. Similarly, section 502(e)(1)(A)(i) of the act considers a drug to be misbranded if its label does not bear the drug's established name, so we cannot allow firms to exclude the drug's established name from the label. Additionally, section 351(a)(1)(B) of the PHS Act requires the package of a biological product to be marked with the product's proper name, the name, address, and applicable license number of the product's manufacturer, and the product's expiration date.

Furthermore, because the rule does not require lot number and expiration date information to be encoded, we decline to allow firms to remove the human-readable lot number and expiration date information from the label.

As for the comment seeking clarification of CPSC requirements, such matters are outside the scope of this rule and outside FDA's jurisdiction.

D. Does the Rule Require a Specific Type of Bar Code? (§ 201.25(c)(1))

1. Should the Rule Require Linear Bar Codes?

Proposed § 201.25(c)(1) would require the bar code to be a linear bar code that meets EAN/UCC standards. The preamble to the March 2003 proposal discussed, in some detail, how we decided to propose the use of linear bar codes and described the tension between trying to create a bar code requirement that would enable hospitals to buy scanning equipment with the confidence that their purchased equipment would not be rendered obsolete by new technology and trying to create a bar code requirement that offered some room for technological innovation (see 68 FR 12500 at 12508 through 12510). We also invited comment on whether we should consider the use of another symbol, standard, or technology, either with or in place of a linear bar code, the acceptance of that other symbol, standard, or technology among parties that would be subject to the rule, and the ability of hospitals to read or use other symbols, standards, or technologies (id. at 12510 and 12529).

(Comment 38) Many comments addressed the subject of linear bar codes. Several comments indicated the rule should require the use of linear bar codes because of their widespread use and because hospitals that are currently printing and scanning bar codes might be unable to upgrade their technology to support nonlinear technologies. One comment stated that our decision to require linear bar codes was ''brilliant'' and that our logic was ''impeccable.'' Another comment said that linear bar codes could be used as an initial requirement and that technology currently installed in most hospitals cannot be upgraded to support nonlinear technologies. The comment added that if we required nonlinear bar codes, hospitals could face significant costs, and those hospitals that had already implemented linear bar code systems would be penalized. Another comment said that many applications of currently-used linear bar code systems are appropriate for suppliers and end users. The comment, which was submitted by a supply company for two large, not-for-profit hospital alliances, added that it shared our concern that ''technologies/standards not be so advanced that hospitals are then unable to read and scan the bar codes,'' and it urged us to evaluate and promote new and emerging technologies ''only as they become more readily available, and easily embraced by end users.''

Another comment said we should require the bar code to meet certain ''attributes;'' the comment explained that this would provide some flexibility (although it did not explain what the attributes would be or what that flexibility was) while still ensuring a minimum standard. The comment added that the standard should be one that does not require hospitals to spend significant amounts of money to replace scanning equipment that would otherwise be acceptable for use. Two comments submitted by drug manufacturers expressed a similar opinion, stating that we should allow firms to use any linear bar code symbology so that firms could pick the symbology that best fits their needs.

One comment agreed with our proposal to require linear bar codes, but asked whether this included multidimensional codes. The comment claimed that multidimensional codes are several thinly-stacked linear codes. It added that, while older bar code scanners might not be able to read multidimensional codes, we should not be concerned about older scanners because most hospitals would not have scanners (and therefore would not need upgrades) or that hospitals with older scanners could upgrade those scanners.

Most comments, however, argued against the use of linear bar codes or asked us to encompass other technologies or to eliminate any reference to linear bar codes in the final rule. Many comments claimed that the rule would discourage or inhibit technological innovation, although they differed as to their preferred alternatives to a linear bar code. For example, one comment said laws and regulations should encourage technological innovation, but did not explain why our particular rule had to do so. Comments opposed to a linear bar code requirement generally advocated the following alternatives:

- Two-dimensional symbologies, on the grounds that such symbologies can be used on small packages, require less space compared to linear bar codes, can encode more data than a linear bar code (although the comments usually did not explain why more data capacity was needed), or can be placed on solid dosage forms themselves. Some comments specifically mentioned DataMatrix as a recommended symbology, whereas others referred to symbols or systems created or marketed by the firm who submitted the comment or to symbols that would be marketed in addition to the two-dimensional symbology. Other comments suggested using two-dimensional symbologies in conjunction with linear bar codes, with the two-dimensional symbology encoding lot number and expiration date information.
- The EAN/UCC system generally, on the grounds that the EAN/UCC system is widely used for drug products, has defined data structures, is used internationally, and would be less expensive compared to a regulatory approach that imposed no standard. However, other comments opposed the EAN/UCC system, declaring it to be ''obsolete,'' or declaring that selecting the EAN/UCC would serve no purpose, would violate unspecified Federal laws, or would create a ''monopoly'' for the UCC. (We discuss comments on the EAN/UCC standard and HIBCC standards in more detail in comment 41 of this document.)
- Radio frequency identification chips. Some comments advocated the use of these chips and claimed that such chips could be an alternative to or used with the bar code and can be ''highly effective'' at identifying individuals and animals in a cost-effective manner. One comment noted that we had mentioned the comparatively high costs associated with radio frequency identification chips, but said we should not reject the chips on cost grounds alone. It said the pharmaceutical industry and health care providers should have the flexibility to choose identification techniques that are the most suited to a product or clinical setting. The comment added that if we required the use of a particular technology, we would create a conflict with our GMP principles because our GMP regulations do not require use of a particular piece of equipment, and we would be creating a disincentive for industry to develop more cost-effective identification systems.
- No standard or symbology at all. These comments advocated the use of ''open'' or ''machine-readable'' requirements so that market forces would decide which technologies would be used. One comment added that the use of nonlinear codes would make linear bar codes technologically obsolete by the time the final rule became effective. Another comment said we should require ''automatic identification'' instead of bar codes. Another comment suggested that manufacturers, repackers, and relabelers be allowed to customize symbols to meet customer needs, although the comment did agree that the NDC number should be present.

Comments were also divided on scanner technology. Most comments that addressed scanner technology declared scanner technology to be a ''non-issue'' because, they claimed, scanners can automatically discriminate between linear bar codes and can be reprogrammed or updated to read specific codes and even complex codes. One comment stated that the adoption rate of two-dimensional image readers is increasing and that such readers are becoming popular and less expensive. Others declared that high-resolution scanners can read both one- and two-dimensional symbologies and predicted that scanner manufacturers and suppliers would become very attentive to customer needs, so that scanner prices would fall. One comment said we should not be concerned about hospital costs at all or not consider such costs as limiting the industry's technological options; the comment argued that our consumer safety mandate precludes financial considerations, and claimed that the OTC drug industry ''rises to the financial challenges presented by government regulations.'' The comment noted that the rule does not require hospitals to buy scanners, so the comment said, ''it seems irrational to tailor these requirements based upon what hospitals may or may not do to ensure the safety of their patients.''

In contrast, two comments indicated that technological limitations do exist. One comment agreed that scanners can read different symbologies, but said that printing technology, particularly with respect to variable information (such as lot number and expiration date), does not exist for high-speed, online printing. Another comment said that technology currently installed in most hospitals cannot be upgraded to support nonlinear symbologies; the comment said that if we required nonlinear bar codes, hospitals could incur significant costs, and those who had adopted bar code systems earlier would be ''penalized.''

(Response) The comments reflect the same array of differing opinions that we encountered at the public meeting and described in the preamble to the March 2003 proposal (see 68 FR 12500 at 12508 and 12509). As we noted in the preamble to the March 2003 proposal, there are two principal, yet contradictory, themes. One theme advocates a specific technology or standard to promote uniformity and to create the conditions under which hospitals could invest confidently in their bar code scanning equipment. The other theme advocates innovation so that newer and perhaps better technologies might be adopted easily. Each theme has its advantages, disadvantages, and assumptions. For example, linear bar codes have the advantage of being a proven, established technology that is easily recognized and easily used. They may also be less expensive than newer, emerging technologies, and are capable of encoding the NDC number. However, linear bar codes have several disadvantages, too, as they offer limited opportunity for innovation and may take up more label space than newer technologies. They also may encode less data compared to other technologies. Thus, if we were to require more data to be encoded on the packaging or labeling for any other reason (such as to allow tracking and tracing of drug products through the drug distribution system), a linear bar code might prove too limiting.

In contrast, a position that advocates innovation, with or without identifying a particular technology, has the potential advantages of encoding more data in a smaller space and perhaps accommodating new technologies as they arise without any additional rulemaking. The disadvantages, however, would include the possibilities that new, emerging technologies may be unproven, not widely accepted, or present unknown risks. For example, current radio frequency identification chips may have less reliable read rates than a linear bar code, and we do not know whether the equipment needed to detect such chips will present EMI issues for other medical devices in the hospital environment. As another example, failure to prescribe a specific technology might deter hospitals and other potential users from buying scanning or reading equipment because there would be no assurance that drug manufacturers would use the same or compatible technologies. As yet another example, requiring ''automatic identification'' of the NDC number could lead some manufacturers to develop their own, exclusive identifiers, and individuals might not recognize those identifiers, particularly if those identifiers are very small, not widely used, or placed under the product's label. Thus, if we were to revise the rule to promote innovation, with or without identifying a particular technology, hospitals and other potential users might be reluctant to purchase scanning or reading equipment, and the rule's benefits would not be fully realized.

After reviewing the comments, we have decided to retain the linear bar code requirement, but will consider revising the rule to accommodate newer technologies as they become more mature and established. Our decision to retain the linear bar code requirement rests largely on the following considerations:

- Linear bar codes are an established and proven technology. They are widely used in many sectors, and we are unaware of any significant problems associated with linear bar codes and their scanners. In contrast, new technologies, such as the radio frequency identification chip, are still being developed or refined, and we do not know, at this time, whether or when those new technologies have or will have widespread acceptance or become standardized, or whether the equipment used to detect or read those new technologies will present any safety or regulatory issues. For example, we do not know whether the equipment needed to detect radio frequency identification chips will present EMI or EMC issues for other devices that are used inside hospitals.
- Linear bar codes are easily recognized and easily used or applied. Most individuals can identify a linear bar code quickly and can scan it without much training. For example, various grocery store chains have installed ''self-scan'' stations where consumers scan the bar codes on their purchases themselves; the consumers are able to do this with little or no training. In contrast, two-dimensional symbologies come in different shapes and sizes, and they can be smaller than linear bar codes. As a result, individuals might not recognize two-dimensional symbologies as quickly and might not even recognize them as encoding data. If the rule allowed any ''automatic identification'' technology, then the risk that individuals might not recognize the technology or lack the proper equipment to read that technology would increase.
- Although most comments opposed the proposed linear bar code requirement, they failed to agree on alternative technologies. For example, some comments supported two-dimensional codes, particularly DataMatrix, but others supported radio frequency identification chips. Some comments endorsed products that a specific company had created, while others suggested that we simply require ''automatic identification'' technology. We believe that if the rule is to result in any significant benefits, it must specify a technology so that hospitals and other interested parties can purchase the correct scanning or reading equipment. We do not agree with the comment that claimed it would be ''irrational to tailor these requirements based upon what hospitals may or may

not do.'' The rule's expected benefits are realized only if hospitals accept and use bar code technology. Therefore, we consider it prudent to consider what hospitals may or may not do when prescribing a regulation that is intended to benefit hospitals and their patients.

We also disagree that the rule prevents or otherwise hinders innovation. Automatic identification technologies are useful in other contexts, such as retail environments, and are used on many different consumer goods. In other words, the fact that the final rule requires the use of linear bar codes does not mean that all progress on other automatic identification technologies must stop, nor does it mean that innovative automatic identification technologies cannot be used on other products.

We recognize that other technologies may be able to encode more data in less space compared to linear bar codes. These arguments do not address the fact that this rule only requires firms to encode one piece of datum (the NDC number). A linear bar code is capable of encoding the 10-digit NDC number. Furthermore, such arguments do not address the principles of regulation that we must observe pursuant to Executive Order 12866; under section 1(b)(5), we are to design our regulations ''in the most cost-effective manner to achieve the regulatory objective'' and to consider ''incentives for innovation, consistency, predictability, the costs of enforcement and compliance * * * flexibility, distributive impacts, and equity.'' Applying that principle to this rule, we believe that a linear bar code is the most ''cost-effective'' device for encoding the NDC number particularly when, as the comments suggest, the alternative would be to specify no technology at all or encompass technologies whose data encoding capacities far exceed the information required. A linear bar code requirement offers consistency, predictability, and lower costs of enforcement and compliance compared to technologies whose acceptance and reliability may be uncertain, or compared to a requirement that offered no criteria upon which hospitals could rely.

We realize that, in October 2003, we issued a report entitled ''FDA Counterfeit Drug Task Force Interim Report'' (see Food and Drug Administration Press Release, ''FDA Anti-Counterfeiting Task Force Interim Report Focuses on High-Tech Weapons and Other New Promising Measures,'' dated October 2, 2003). This report discussed, among other things, anti-counterfeiting technologies, including ''track and trace technologies.'' The final rule does not affect the development or adoption of such ''track and trace technologies.'' Moreover, the final rule's underlying purpose (prevention of medication errors) is distinct from the purposes underlying anti-counterfeiting efforts (preventing the introduction of counterfeit drugs, facilitating identification of counterfeit drugs, minimizing consumer risk and exposure to counterfeit drugs, and avoidance of unnecessary costs on the prescription drug system). For example, in the medication error prevention context, the goal is to ensure that the right drug, in the right dose and right route of administration, is given to the right patient at the right time, so requiring a bar code on a unit-dose product is both necessary and appropriate, but information regarding the drug's origin (i.e., place of manufacture) is not essential. In contrast, for track and trace purposes, the goal is to ensure that individual products can be followed through the drug distribution system from the point of manufacture, but this goal does not necessarily extend down to the unit-dose package level.

Nevertheless, we reiterate that we will consider revising the rule to accommodate new technologies. As we explain in more detail in section II.I of this document, we expect compliance with the bar code requirement within 2 years after the final rule's effective date. At that time, we will begin examining other automatic identification technologies to determine whether we should amend the rule to allow the use of such technologies. We intend to conduct our examination in a public and transparent manner, with opportunity for public participation and comment. This could be done, for example, through a public meeting, a document inviting comment, an advance notice of proposed rulemaking, or other public forum. We will decide on the appropriate public forum at a future time.

Regarding the EAN/UCC system, the final rule allows the use of either EAN/UCC or HIBCC standards. We discuss the reasons behind this change at comment 41 of this document.

As for the comment concerning multidimensional codes, we note that there is disagreement whether certain symbologies are two-dimensional or simply a series of thin, one-dimensional codes stacked upon each other. Therefore, we cannot say, as a general matter, whether multidimensional codes are ''linear bar codes'' within this final rule because we cannot be sure that all parties share the same interpretation as to what constitutes a multidimensional code. Nevertheless, if a firm believes that a particular type of thin, one-dimensional codes that are stacked upon each other is still a ''linear bar code'' and intends to use that stacked code, that stacked code must be capable of being read clearly by scanning or reading equipment in the same manner as conventional linear bar codes to fall within § 201.25(c).

Finally, regarding one comment's claim that a linear bar code requirement would create a conflict with our GMP principles and will create a disincentive for industry development of other identification systems, we disagree. The linear bar code is not a manufacturing process; it is instead the visual representation of information. To use an analogy, we require labels to use the English language except where the article is to be distributed solely in the Commonwealth of Puerto Rico or in a U.S. Territory where the predominant language is not English (see 21 CFR 201.15(c)(1)). The English word is the visual representation of the information. If we had to accept any language on product labels (using the comment's GMP theory), then those using the product might not understand the information if they did not know the language used on the label. Furthermore, as we stated earlier in this response, the linear bar code requirement does not prevent anyone from developing innovative automatic identification technologies for any other industry for any other reason, and we will consider whether to accept other automatic identification technologies as they become more mature and accepted.

(Comment 39) One comment claimed it would be ''legally indefensible'' for hospitals to not choose two-dimensional systems if firms encoded lot number and expiration date information; the same comment also declared that some hospitals have their suppliers use two-dimensional codes so requiring linear bar codes would ''force'' those hospitals to ''abandon'' their systems because their suppliers would have to convert to linear bar codes.

(Response) We disagree with the comment. The only required piece of encoded data is the NDC number; hospitals are free to decide which scanning systems are best for them and are also free to decide whether to take advantage of any voluntarily-encoded lot number and expiration date information. We reiterate that we were unable to demonstrate that the benefits of encoding lot number and expiration date information would exceed the costs (see 68 FR 12500 at 12528 and 12529). Therefore, we disagree that it would be ''legally indefensible'' for hospitals to choose linear bar code scanners that are

perfectly capable of reading the NDC number contained in a linear bar code.

We also disagree that the final rule ''forces'' hospitals to abandon systems that they may have adopted before this rulemaking. If a two-dimensional scanning system is capable of reading both one- and two-dimensional symbologies, then the system should still be able to read the NDC number contained in the one-dimensional, linear bar code. We acknowledge, however, that if a hospital had insisted that its suppliers use only two-dimensional codes, the final rule's linear bar code requirement means that those suppliers must use a linear bar code to encode the NDC number. If the supplier wishes, it can encode lot number and expiration date information voluntarily using any symbology or automatic identification technology, so if the hospital insisted that the supplier use two-dimensional symbologies to encode lot number and expiration date information, the hospital's two-dimensional scanning system would still be useful.

(Comment 40) One comment asked whether ''linear bar code'' meant to include a specific symbology called ''RSS–14 stacked.'' The comment explained that RSS–14 stacked ''is essentially the same thing as RSS–14, except that it is printed in two rows in order to make it narrower at the expense of height.'' The comment said that a scanner can easily decode an RSS–14 stacked symbol, but added that, ''I hope you get input from Scanner manufacturers on this point.''

(Response) The comment is correct that RSS–14 stacked is a variant of the RSS–14 linear bar code and that it consists of two rows of two segments each. A ''separator pattern'' is printed between the two rows to eliminate cross-row scanning errors.

We believe that RSS–14 stacked symbology can be read by linear bar code scanners, although the scanners would have to be programmed to read RSS–14 codes and, depending on the scanner, may require more time to read a stacked code. Thus, we would consider RSS–14 stacked to be a linear bar code within the rule.

(Comment 41) Some comments questioned or criticized the proposed rule's reference to UCC standards. One comment said that ''standards'' refers to the data structure and not to symbologies. The comment asked if we meant that the linear bar code had to be one used by the UCC and that the NDC number had to be in a UCC data format.

One comment, submitted by a medical device trade association, supported use of either the EAN.UCC or HIBCC standards. The comment explained that most medical device manufacturers who are voluntarily labeling their products use the UPN system, and the EAN.UCC and HIBCC standards comprise the UPN system. HIBCC also recommended that the final rule not rely solely on EAN.UCC standards; it acknowledged that EAN.UCC standards are ''by far the most prevalent in pharmaceutical labeling,'' but suggested that alphanumeric coding (which HIBCC standards use) ''allows for literally-encoded information that is inherently safer'' (than numeric coding alone).

HIBCC, as well as another comment, also stated that requiring EAN.UCC standards would create a monopolistic environment that might inhibit the development and implementation of technologies outside the EAN.UCC's purview. The other comment claimed that the UCC is not a standards body, has proprietary interests, provides sponsored bar codes to members as part of a variable annual fee, and that the linear bar codes that would be used on hospital patient identification bands are not EAN.UCC codes, so that there would be no benefit in selecting EAN.UCC standards. The comment protested that the EAN.UCC standard requirement would compel manufacturers to join the UCC even though adequate bar codes are available in the public domain, and declared that the rule would violate unnamed Federal laws by referring to EAN.UCC standards.

Another comment advocated use of both EAN.UCC and HIBCC standards. It suggested that this would encourage the adoption of automatic identification technologies as they develop, although the comment also recommended that linear bar codes be the initial technological requirement so that hospitals that have bar code systems are not disadvantaged.

(Response) Proposed § 201.25(c)(1)'s reference to UCC.EAN ''standards'' was intended to mean that the linear bar code had to be one that the UCC recognized and the data standard had to be in a UCC.EAN format (see 68 FR 12500 at 12509).

However, after considering the comments, we will interpret § 201.25(c)(1) as meaning that the linear bar code can be in any format, and the final rule gives firms the option of using EAN.UCC or HIBCC data standards. (We have revised the rule to refer to ''EAN.UCC'' standards, rather than ''UCC/EAN'' standards, in order to use the commonly-recognized abbreviation.) In other words, the manner in which the NDC number is encoded may be in an EAN.UCC or HIBCC format, and the manner in which the NDC number is visually presented must be a linear bar code. We have decided to give firms the option of using HIBCC data formats because HIBCC is a widely-recognized, nonprofit standards development organization whose standards, like EAN.UCC standards, are accredited by ANSI, and, as the comments suggested, allowing the use of either EAN.UCC or HIBCC standards may encourage further development and adoption of other automatic identification technologies. We also cannot preclude the possibility that some firms may prefer using alphanumeric code formats, which HIBCC uses, although we do not express any opinion as to whether alphanumeric codes are ''safer'' than numeric ones.

Allowing the use of HIBCC standards will also prevent the creation of the ''monopolistic'' environment that some comments feared. Although one comment claimed that the UCC is not a standards organization and implied that the UCC will benefit financially if we require bar codes to use EAN.UCC standards, our information is that the UCC is a not-for-profit standards organization.

We strongly recommend that manufacturers, repackers, relabelers, and private label distributors who are subject to the bar code requirement carefully consider their linear bar code symbology and standard choices. (The EAN.UCC or HIBCC standard may also determine the type of linear bar code symbology that is used.) The bar code's ability to affect medication error rates depends largely on the ability of hospitals to scan and interpret the data in the bar code. So, for example, choosing a commonly-used linear bar code symbology in a standard that scanners can easily read will have a greater impact on patient safety compared to a unique bar code symbology that few (if any) scanners are programmed to read.

2. Should the Rule Impose Any Conditions on the Bar Code?

Proposed § 201.25(c)(1)(i) and (c)(1)(ii) would require the bar code to be surrounded by sufficient blank space so that the bar code can be scanned correctly and require the bar code to remain intact under normal conditions of use. The preamble to the March 2003 proposal explained that some manufacturers had placed bar codes at locations where the bar codes are destroyed, damaged, or otherwise rendered useless (see 68 FR 12500 at 12510), so the proposal was intended to help ensure that the bar codes could be read correctly.

(Comment 42) One comment asked whether our reference to ''blank space'' referred to ''quiet zones'' in a bar code. A ''quiet zone'' in a bar code usually refers to a blank space that appears before the first bar and after the last bar.

(Response) Section 201.25(c)(1)(i)'s reference to ''blank space'' means that the linear bar code must be surrounded, on all four sides, by an area where no print occurs. This is slightly different from the ''quiet zone'' in a bar code because § 201.25(c)(1)(i)'s ''blank space'' would include areas that are above and below the bars.

We note, however, that we have previously indicated that we would not object if firms voluntarily encoded lot number and expiration date information (see 68 FR 12500 at 12508) and that such voluntarily-encoded information might appear in another machine-readable format with the linear bar code. For example, a firm might decide to use a composite code, where the NDC number is encoded in a linear bar code and the lot number and expiration date information is encoded in a two-dimensional code, with the two-dimensional component placed immediately above the linear bar code. If a firm elects to encode lot number and expiration date information voluntarily, and the voluntarily-encoded information is immediately adjacent to the required linear bar code, we will interpret the ''blank space'' requirement as applying to the entire composite code. In other words, we would not interpret the ''blank space'' requirement as preventing firms from using composite codes.

(Comment 43) One comment disagreed with proposed § 201.25(c)(1)(ii) insofar as it would require the bar code to remain intact under normal conditions of use. The comment said manufacturers should be allowed to print bar codes across perforations on blister packs as long as this did not affect the ability of the bar code to be scanned correctly. The comment said that printing the bar code across perforations would leave more space on the drug's label for other required information.

In contrast, another comment, submitted by a hospital, stated that the hospital's use of manufacturers' bar codes suggests that those codes sometimes fail to maintain their integrity. The comment said that linear lines become jagged, the markings degrade on the medium on which they are placed, or the bar code is placed in such a manner that it becomes unusable at the unit-dose level. The comment added that ''it has been our experience that the bar code does not always agree with the written description of the product,'' and it said that we should continue to require the bar code to remain intact under normal conditions of use, particularly with respect to unit-dose packages.

(Response) Section 201.25(c)(1)(ii) requires the bar code to remain intact under normal conditions of use. Our fundamental goal is to reduce or prevent medication errors, and that goal is best served when the bar code remains intact under normal conditions of use. As we stated in the preamble to the March 2003 proposal, partial or incomplete bar codes can provide misleading information or not be read at all by scanners (see 68 FR 12500 at 12510); these potential problems are avoided if the bar code remains intact under normal conditions of use.

We realize that label space can be limited due to other information that our statutes or regulations require to be on a drug's label, but there may be alternatives to printing the bar code across perforations. For example, the final rule does not require the bar code to appear on the same surface as other label information. Likewise, the final rule does not prevent a manufacturer, repacker, relabeler, or private label distributor from revising its packaging to accommodate more label information. Thus, there may be other approaches that would ensure that the bar code remains intact under normal conditions of use.

E. Where Does the Bar Code Go? (§ 201.25(c)(2))

Proposed § 201.25(c)(2) would have the bar code appear on the drug's label as defined by section 201(k) of the act. The preamble to the March 2003 proposal explained that section 201(k) of the act defines ''label'' as:

> a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

Thus, by proposing to require the bar code to be on the drug's label, proposed § 201.25(c)(2) would result in bar codes on the drug's immediate container label as well as the outside container or wrapper, unless the bar code is easily legible and machine-readable through the outside container or wrapper (see 68 FR 12500 at 12511).

(Comment 44) One comment asked that we require the bar code to ''be oriented on the label in such a way as to promote visual reading of the drug, strength, etc. while scanning the bar code.'' The comment explained that positioning the bar code in any other way would make users dependent on the scanning process instead of reading the drug's label. The comment said the only exception to its suggested placement restriction should be when the label does not support the bar code format, ''with the burden on the manufacturer to justify the decision not to orient the label contents in this fashion.''

(Response) We decline to revise the rule as suggested by the comment. By not specifying how or where the bar code must appear, the rule gives firms considerable flexibility in designing their labels to include the bar code and any other information required by law or FDA regulations.

Although we recognize the comment's concern about relying too much on technology, we disagree with the comment's assumption that users will become dependent on the bar code and will stop reading drug labels. The human-readable information on a drug's label goes far beyond the drug's NDC number. For example, under § 201.100(d)(1), a drug's labeling, whether or not it is on or within a package from which the drug is to be dispensed, must contain adequate information for the drug's use, including any relevant warnings, hazards, contraindications, side effects, and precautions; the drug's NDC number will not provide such information. As another example, section 502(b)(1) of the act declares a drug to be misbranded if its label does not contain the name and place of business of the manufacturer, packer, or distributor, while section 502(e)(1)(A) declares a product to be misbranded if its label does not contain the drug's established name, quantity or proportion of each active ingredient. In short, the bar code, and the NDC number contained in the bar code, act more as a link between the drug, the patient, and the patient's drug regimen and do not act as a surrogate for the drug's label.

(Comment 45) One comment focused on products that are individually packaged in a tray or pouch and are considered sterile within the tray or pouch. The comment said we should allow the bar code to be placed on the tray or pouch because the drug is supposed to remain sterile and not be removed from the tray or pouch until the time the drug is administered.

(Response) We decline to revise the rule as suggested by the comment. By requiring the bar code to appear on the

product's ''label,'' § 201.25(c)(2) should result in a bar code on the immediate container label and the outer wrapper label. We are aware that, despite labeling instructions to the contrary, individuals might remove the outer wrapper and administer the drug product at a later time. Therefore, a bar code on the immediate container label may help prevent product mixups and medication errors that may occur when the drug product is removed from the outer wrapper and not used immediately.

As for the comment's drug sterility concern, we are not aware of any reason why including a bar code on the immediate container label as well as on the outer wrapper would adversely impact drug product sterility.

(Comment 46) Some comments focused on drug packaging. Some comments asked us to require bar codes on every unit-of-use package so that hospitals do not need to repack drugs. Several comments said we should require single dose packaging to make bar coding easier and accurate dosages more feasible. A different comment said that we should require manufacturers to have unit-dose packaging before they can market a drug. Other comments expressed concern that a bar code requirement might lead manufacturers to stop unit-dose or unit-of-use packaging or insisted that manufacturers use such packaging. Another comment asked us to require bar codes on ''all packaging'' as soon as possible, but a different comment agreed that we should require bar codes on unit-dose packages.

(Response) Regarding unit-of-use packages, the rule does require bar codes on such packages because § 201.25(c)(2) states that the bar code must appear on the drug's label. Section 201(k) of the act defines ''label,'' in part, as ''a display of written, printed, or graphic matter upon the immediate container of any article.'' Thus, because a unit-of-use package would be the immediate container for a drug, the unit-of-use package must bear a label and, under § 201.25(c)(2), have a bar code.

We decline to require manufacturers to use unit-dose or unit-of-use packaging. We recognize that concerns may exist over the rule's impact on such packaging, and we even raised the issue ourselves in our public meeting (see 67 FR 41360 at 41361). However, as we noted in the preamble to the March 2003 proposal, our industry contacts suggest that the costs associated with a bar code requirement ''would not be great enough to significantly impact the market'' and that ''the expected reduction in hospital over-packaging could increase market demand for unit-dose products despite the cost difference'' (see 68 FR 12500 at 12526). In other words, our industry contacts suggest that unit-of-use or unit-dose packaging decisions depend more on market demand than on bar code costs.

We also decline to require bar codes on ''all packaging.'' The preamble to the March 2003 proposal explained that requiring every package to bear a bar code would result in too many packages being bar coded regardless of the potential impact—or absence of impact—on medication errors. For example, we explained that requiring bar codes on every package would mean that a shipping container would have a bar code, yet no hospital would dispense a drug directly from a shipping container to a patient (see 68 FR 12500 at 12511). We maintain that requiring bar codes on all packages would not be helpful insofar as medication errors are concerned.

(Comment 47) One comment said that medicated creams and ointments can now be reduced from multidose tubes to single dose units and that some drugs have specific dosage requirements that further support the use of single dose packaging to mitigate dosing errors. The comment asked what is being done to convert packaging of semi-solids into ''the needed single dose units.''

(Response) Issues regarding the production of unit-dose packaging, regardless of whether the drug is a liquid, cream, or solid, are outside the scope of this rule.

(Comment 48) One comment discussed how bar codes can be imprinted on pills. It described a system that uses images of the drug on medication schedules, prints bar codes on the drugs themselves, and uses two-dimensional bar codes with a ''human recognizable icon or symbol'' that identifies the ''general type of pill.''

Another comment said we should consider technologies that allow one- or two-dimensional bar codes to be printed on color film coated tablets and other solid oral dosage forms. It added that covert marking systems could also be used to address drug counterfeiting concerns, and printing codes on the drugs themselves could reduce unit-dose packaging requirements.

(Response) We decline to allow the bar codes to be printed on tablets and other solid oral dosage forms. As we stated in our response to comment 3 in section II.B.1 of this document, 21 CFR part 206 requires imprinting on solid oral dosage forms. The imprint was designed to help identify solid oral dosage forms, particularly in emergency situations, and to help consumers and health care professionals identify drugs (see 58 FR 47948; 21 CFR part 206). If we allowed the bar code to be imprinted directly on a pill, the bar code might interfere with that drug's imprint and could force health care professionals and hospitals to consult two different databases (one on drug imprint codes and another on bar codes) to determine which drug they had before them.

Imprinting a bar code on a drug may also raise drug stability issues or affect a drug's dissolution rate. Imprinting bar codes on tablets has other practical limitations; for example, the same imprinting approach cannot be used for drugs that are in liquid, gaseous, or semi-solid form.

As for covert marking systems and counterfeiting concerns, such matters are outside the scope of this rule.

F. Must Blood and Blood Components Bear ''Machine-Readable'' Information? (§ 606.121(c)(13))

Current FDA regulations, at 21 CFR 606.121(c)(13), state that the container label for blood and blood components ''may bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research.'' The proposed rule would amend § 606.121(c)(13) to require the use of ''machine-readable information'' in a format approved by the Director of the Center for Biologics Evaluation and Research (CBER) (the CBER Director). The CBER Director would review the machine-readable information technology to ensure that the minimum requirements are met regarding the accuracy of the required labeling information, spacing, and conditions of use.

Proposed § 606.121(c)(13) also would:

- Explain that all blood establishments that manufacture, process, repackage, or relabel blood or blood components intended for transfusion and regulated under the act or the PHS Act are subject to the machine-readable information requirement;
- State that blood and blood components intended for transfusion are subject to the machine-readable information requirement;
- Describe the minimum contents of the machine-readable information as a unique facility identifier, lot number relating to the donor, product code, and the donor's ABO blood group and Rh type;
- Specify that the machine-readable information must be unique to the blood or blood component, be surrounded by sufficient blank space so that the

machine-readable information can be read correctly, and remain intact under normal conditions of use; and

• State that the machine-readable information must appear on the label of the blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

The proposal would not specify where the machine-readable information must appear on the label. As the preamble to the proposed rule explained, unlike the situation for other drugs, there is already substantial use of bar codes, notably ABC Codabar and ISBT 128, for blood and blood components (see 68 FR 12500 at 12512).

The preamble to the proposed rule invited comment on whether we should specify the use of ABC Codabar, ISBT 128, a different symbology or standard, or simply require the use of ''machine-readable information'' approved by the CBER Director (id.). We also invited comment on whether a ''machine-readable information'' approach was feasible or whether we should require the use of EAN.UCC standards for blood and blood components.

(Comment 49) Many comments urged us to require the use of ISBT 128 rather than ''machine-readable information.'' The comments referred to ISBT 128's international acceptance, ''negligible'' licensing and registration costs, superiority to Codabar, and acceptance by FDA, community blood centers, hospital blood banks, and other parties. Some comments pointed out that ISBT 128 is a data standard rather than a specific bar code; thus, to these comments, requiring ISBT 128 would cover newer machine-readable technologies, including two-dimensional symbols and radio frequency identification chips. One comment said that a failure to require ISBT 128 would hinder software development because software could use the identifiers and check digits in ISBT 128.

Other comments opposed requiring the use of ISBT 128 or suggested a different standard. One comment said that requiring ISBT 128 would force FDA to engage in new rulemaking if we decided that a new technology should be adopted. The comment did state, however, that if a single standard must be developed, it would support ISBT 128. Another comment, submitted by the UCC, said that EAN.UCC standards are used in commercial packages for shipping and receiving blood products; the comment said that if the blood products community requested it, the UCC would support creating bar code guidelines for blood products based on the EAN.UCC system. The comment added that Japan uses the EAN.UCC system for its blood components. Similarly, another comment said that the bar codes for blood components should be the same as those used on prescription and OTC drug products because pharmacies distribute blood components and nurses administer them.

(Response) The final rule retains the ''machine-readable information'' language with a clarification that the format, and not the actual information, must be approved by the CBER Director. This will enable § 606.121(c)(13) to accommodate changes in machine-readable technologies. For example, FDA recognized the use of Codabar (a specific bar code symbology) in 1985, and, in 2000, accepted the use of ISBT 128, version 1.2.0. More importantly, unlike the situation for other prescription drugs, there is already substantial consensus on the use of machine-readable symbols on blood and blood component labels. If we were to amend the rule to require the use of ISBT 128, we would ensure a uniform bar coding standard for blood and blood components and be consistent with the existing international standard, but we would also have to engage in new rulemaking if the international consensus standard changed to adopt a new symbology, standard, or technology. We believe that relying on an international consensus standard and requiring ''machine-readable'' information in a format approved by the CBER Director allows us to maintain uniformity in the symbologies or technologies used and accommodate new technologies in the future. We will announce, through guidance documents, our thinking and recommendations about acceptable technologies. In deciding whether a particular technology is acceptable for blood and blood component container labels, we will review the technology to ensure that the minimum requirements are met regarding the accuracy of the required labeling information, spacing, and conditions of use. We anticipate that the blood industry will standardize encoded machine-readable information and reading equipment, using our guidances to minimize, to the greatest extent possible, the need for ''country-specific'' software and the high cost associated with software development and maintenance.

We also decline to require the use of EAN.UCC standards on blood and blood component container labels. The blood industry currently uses a machine-readable code that does not meet EAN.UCC standards. If an EAN.UCC standard were implemented, it would require an overhaul of the United States blood industry and the international blood industry (because the resulting standard would depart from ISBT 128). We believe such an impact to be unnecessary given our understanding that bar code scanners can be programmed to recognize different symbologies.

Additionally, on our own initiative, we have revised § 606.121(c)(13)(i) to replace the word ''repackage'' with ''repack.'' ''Repack'' is the preferred term to describe the act of putting a product into a different container.

(Comment 50) One comment said that the type of bar code was not as important as the underlying information contained in the code. The comment wanted to be able to track lot or donation numbers, the manufacturer's license number, country code, information about the blood group, product type, any modifications or special information, and dosage.

(Response) Section 606.121(c)(13)(iii) requires the machine-readable information for blood and blood components to contain, at a minimum,

• A unique facility identifier;
• lot number relating to the donor;
• product code; and
• ABO and Rh of the donor.

Thus, some information sought by the comment would already be required. Other pieces of information are also covered under ISBT 128. For example, ISBT 128 contains a ''donation identification number;'' this number can identify the country/collection facility, the year the donation was made, and a serial number associated with the donation. ISBT 128 also has an optional ''special testing'' field to convey the results of special or additional testing.

Although the comment also mentioned ''dosage'' information, dosage is not normally an issue for blood and blood components, so we decline to require dosage information as part of the machine-readable information for blood and blood components.

(Comment 51) The preamble to the proposed rule asked how the rule might affect hospitals where patients receive blood or blood components, particularly with respect to a hospital's decision to purchase a machine reader for blood and blood component codes and the linear bar codes on drugs and certain OTC drug products (see 68 FR 12500 at 12529).

We received several different opinions on this subject. One comment said that if hospitals had to change their blood and blood component coding systems to use EAN.UCC standards, it

would take ''years'' to develop data structures, change transfusion software, and implement the changes, and this would be a setback for industry standardization. In contrast, another comment, submitted by the UCC, said there would be little or no effect on hospitals because scanners can read multiple codes, and so use of the EAN.UCC system on all products would simplify software development and maintenance. It added that we should examine the cost of maintaining two standards (EAN.UCC and ISBT 128) within the global marketplace and any potential disruption if ISBT 128 were abandoned in favor of the EAN.UCC system.

Three comments said that ISBT 128 could be easily compatible with any bar code system. The comments said that software systems developed for blood centers and many hospital blood banks are already ''ISBT 128 ready.''

(Response) As we stated in our response to comment 49 in section II. F of this document, we decline to require the use of EAN.UCC standards on blood and blood component container labels. We agree with those comments stating that bar code scanners can be programmed to recognize ISBT 128 in addition to other symbologies, and requiring the blood industry to convert to EAN.UCC standards would affect efforts to adopt uniform standards within the United States and the international blood industry.

(Comment 52) One comment asked if ''blood component''included intravenous immune globulin (IGIV) and albumin. The comment felt that ISBT 128 and the data that would be encoded for blood components are inappropriate for IGIV and albumin. The comment added that IGIV and albumin are distributed by pharmacies and administered by nurses, so they should be treated like other drugs.

(Response) IGIV and albumin are therapeutic products that would be subject to the bar code requirement for drug products through § 610.67. In other words, IGIV and albumin are not subject to the bar code requirements for blood and blood components, but they are subject to the bar code requirements for drug products.

(Comment 53) One comment asked us to clarify whether source plasma used to manufacture plasma-derived therapies is subject to a bar code requirement. The comment said that Source Plasma, when not intended for use as a final dosage product, should not be subject to the bar code requirement.

(Response) Source Plasma is not subject to the bar code requirements. As stated in § 606.121(a), the container label requirements for blood and blood components are not applicable to Source Plasma. The machine-readable requirements apply only to blood and blood components intended for transfusion (see § 606.121(c)(13)). Because Source Plasma is intended as source material for further manufacturing use (see § 640.60 (21 CFR 640.60)) and is not intended for transfusion, Source Plasma does not fall within the bar code requirement.

(Comment 54) Two comments suggested that we require bar codes on certain medical devices such as blood bags, filters, and apheresis kits.

(Response) We decline to adopt the comments' suggestion. As we stated in our response to comment 29 above, medical devices present different regulatory issues and challenges compared to drugs, and, unlike drugs, medical devices do not have a unique, reliable identifying number. Consequently, we continue to omit medical devices from the final rule.

G. Must Biological Products Have a Bar Code? (§ 610.67)

The proposed rule would require biological products (other than devices, blood, and blood components intended for transfusion) to comply with the bar code requirements at § 201.25.

We received no comments that were specific to § 610.67. However, on our own initiative, we have revised § 610.67 to clarify that the bar code requirement at § 201.25 does not apply to devices that are regulated by CBER (such as devices that are the subject to the biologics licensing application (BLA), premarket approval (PMA) application, or 510(k) requirements), or to blood and blood components intended for transfusion. As we explained in section II.B.5 of this document, devices are exempt from the bar code requirements, whereas blood and blood components intended for transfusion are subject to the ''machine-readable'' information requirements at § 606.121(c)(13).

H. What Other Comments Did We Receive?

Many comments were not directed at any particular provision but instead asked procedural questions (such as how bar code information should be reported to us), asked us to create more documents (particularly with respect to bar code quality), or discussed whether we should keep these regulations in effect after bar coding, for medication error purposes, became widespread. We discuss these comments in this section.

1. Comments Seeking More Action by FDA

(Comment 55) The preamble to the proposed rule stated that firms whose drug products are already approved or marketed could notify us about the addition of a bar code to their product labels through an annual report (see 68 FR 12500 at 12512).

One comment disagreed, stating that we should apply standard reporting requirements for such label changes. It said that annual reports are not sufficient to provide the maximum benefit to those using the bar codes. It suggested that certain third-party databases might be able to create new data fields that provide information on drugs and drug packaging on a ''very frequent'' basis.

(Response) The comment misunderstood our position. When we referred to the annual report, we meant that firms whose drug products have already been approved would simply notify us that they had added a bar code to their package labels; that notification to FDA could occur on an annual basis. Annual reports are commonly used to report minor label changes to us.

As for transferring information regarding NDC numbers to databases (which bar code scanners and hospital computers might consult in order to decipher the bar code), we routinely make such information available. Moreover, as we stated in the preamble to the proposed rule, we are collaborating with the National Library of Medicine and the Department of Veterans Affairs to create a collection of up-to-date, computer-readable electronic labels for marketed drug products (see 68 FR 12500 at 12511). This collaboration contemplates daily updates of information and, as a result, constant updates of new NDC numbers.

In short, we intend to make NDC number information available to databases constantly. We do not intend to release NDC number information only once per year.

(Comment 56) Several comments asked us to draft additional documents. For example, one comment said we should issue a guidance document to instruct hospitals and others to use the same bar coding methods and principles that manufacturers use if hospitals and other entities decide to bar code or to repack drugs. Another comment suggested that we should issue a guidance document advising firms on how to encode lot number and expiration date information if they choose to do so voluntarily.

(Response) We decline to create the guidance documents that the comments

sought. In general, hospitals are exempt from the bar code requirements, and so we believe that our resources are better spent developing regulatory materials, when appropriate, for regulated entities. Additionally, we lack sufficient expertise to advise interested parties on bar coding methods and equipment, but we believe there are sufficient documents and standards issued by third parties such that, at this time, we do not need to generate such documents or standards ourselves.

(Comment 57) One comment asked us to provide expedited review of pre-market submissions for blood establishment computer software. The comment said that software users must validate software upgrades before such improvements are applied to patient care, but said that validation would require extensive time.

(Response) We decline, in this rulemaking, to provide for expedited review of premarket submissions for blood establishment computer software. The current rulemaking is aimed at describing the bar coding requirements for drugs and similar ''machine-readable'' information requirements for blood and blood components. In the absence of any submissions, it would be both premature and beyond the scope of the current effort to address requests for expedited PMA reviews for blood establishment software. However, in this regard, we have made available a ''Reviewer Guidance for a Premarket Notification Submission for Blood Establishment Computer Software'' on January 13, 1997, and comments on FDA guidance may be submitted at any time to the contact listed in that guidance.

(Comment 58) One comment asked us to create an expedited submission category for packaging changes that would be needed to comply with a bar code requirement. The comment predicted that many firms would submit supplemental applications to us so that we might approve packaging changes, and the comment predicted that a large number of supplemental applications would prevent us from approving packaging changes quickly.

(Response) We decline to adopt the comment's suggestion. We interpret the comment as suggesting that we may need to expedite review of supplemental applications regarding packaging changes and that the comment's use of the word, ''expedited,'' means that we should take such supplemental applications out of the normal review process and review them first, regardless of the order in which they arrived relative to other types of applications.

We do not believe that expedited review will be necessary for several reasons. First, most packaging changes that would be done to accommodate a bar code should not require prior FDA approval. Packaging changes can be reported to us in various ways, through a supplement of changes being effected (see 21 CFR 314.70(c)), a supplement of changes being effected in 30 days (see § 314.70(g)(2)), and an annual report (see § 314.70(g)(3)); none of these supplements or reports require prior FDA approval.

Second, for drugs that have already received FDA approval by the time of the final rule's effective date, we are giving such drugs 2 years to comply with the bar code requirement. If a firm believes that its packaging change is of a type that needs prior FDA approval, this 2-year period should give the firm and FDA sufficient time to prepare and review the supplement.

If a firm still believes that it needs expedited review of a packaging change, we would consider such requests under our existing regulations and procedures (see § 314.70(b); Center for Drug Evaluation and Research, ''Requests for Expedited Review of Supplements to Approved ANDA's and AADA's,'' Manual of Policies and Procedures (MAPP) 5240.1 (dated November 1, 1995)); Center for Drug Evaluation and Research, ''Requests for Expedited Review of NDA Chemistry Supplements,'' MAPP 5310.3 (dated June 11, 1999)). Under § 314.70(b), applicants may ask for expedited review of a supplement if a delay in making the change would impose an ''extraordinary hardship'' on the applicant, and we consider expedited review requests on a case-by-case basis and undertake such expedited reviews if adequate review resources are available.

For packaging changes involving a biological product, see 21 CFR 601.12 and 314.70.

2. Comments Relating to Bar Code Problems or Quality

(Comment 59) One comment asked how people might report bar coding and scanning errors.

(Response) As we stated in the preamble to the proposed rule (see 68 FR 12500 at 12510), the bar code would be part of the drug's label, so errors in applying the bar code to the label should be handled like any other packaging or labeling operation problem under GMPs (see 21 CFR 211.122, 211.125, 211.130, 211.180, and 211.184)).

If an individual encounters a problem scanning the bar code, and the problem is due to the bar code's quality, then such scanning problems can be reported to FDA through the Drug Quality Reporting System. The Drug Quality Reporting System encourages health care professionals to voluntarily report observed or suspected defects or quality problems with marketed drug products. The agency receives reports through the MedWatch Program.

For biological products, manufacturers can report scanning problems as biological product deviations under existing reporting procedures (see 21 CFR 600.14 and 606.171).

(Comment 60) Some comments asked us to audit or monitor bar code quality. One comment said we should require the bar code to maintain a passing grade of C or better to ensure its quality.

(Response) As we noted in the preamble to the proposed rule, various bar code standards exist, as do standard procedures for bar code verification (see 68 FR 12500 at 12510–12511). Given these standards and other documents, as well as the comparatively greater expertise of standards organizations such as the American Society for Testing and Materials and the International Organization for Standardization, we do not intend to audit or monitor bar code quality aggressively. We also believe that our GMP requirements and the Drug Quality Reporting System provide additional safeguards to ensure bar code quality.

3. Comments Regarding FDA's Future Involvement With Bar Codes

(Comment 61) Two comments discussed our future involvement with a bar code requirement. One comment said that if the rule referred to EAN.UCC standards, without specifying the use of linear bar codes, we would not need an ''exit strategy'' to allow for future technologies and innovation.

In contrast, another comment said that the proposed rule had gained the pharmaceutical industry's attention and that there is ''considerable momentum'' towards putting bar codes on drugs. The comment said this voluntary effort would continue even if we did not issue a final rule and said that the market would decide which automatic identifiers meet health care needs so that we no longer had to be involved. The comment said our continued involvement in this area would not be ''efficient;'' it said we could monitor progress towards the use of automatic identifiers, but should not manage it. It also suggested that we include a ''sunset'' date in the final rule because it claimed the rule created ''enormous uncertainty'' for hospitals because the rule permitted inclusion of other

information in other formats. Thus, if a ''sunset''date existed, manufacturers would be able to use any one- or two-dimensional code after that date, and this would give all parties ''a fair opportunity to invest in the technology that will meet the future needs of their institutions.''

(Response) As we stated earlier in our response to comment 38 in section II.D.1 of this document, we intend to revisit technological issues in the future, but we believe that linear bar codes, as an initial requirement, will help prevent or reduce medication errors.

We agree, in part, with the comment that suggested that market forces could reduce the need for continued FDA involvement. We note that, for blood and blood components, interested parties have been able to agree on domestic and international standards for encoding certain information. For example, ABC Codabar is a bar coding system that the health care industry adopted for blood and blood components and is still commonly used in the United States. ISBT 128 is the product of a consensus conference held by the International Council for Commonality in Blood Bank Automation and is now preferred over ABC Codabar. The use and acceptance of ABC Codabar and ISBT 128 demonstrates that interested parties can agree on specific data standards and formats and, more importantly, use those standards and formats.

Unfortunately, as the comments to the July 26, 2002, public meeting and the proposed rule demonstrate, consensus is either absent or, at best, is still developing when it comes to bar codes or automatic identifiers for drugs. We continue to encourage manufacturers, repackers, relabelers, private label distributors, hospitals, scanning or reading equipment manufacturers, and other interested parties to explore avenues for greater cooperation and consensus. We believe that all parties may benefit by reducing medication errors through the use of bar codes or other automatic identification technologies. For example, manufacturers and hospitals may see fewer medication errors and, as a result, reduced liability. Patient safety would be enhanced as patients would experience fewer medication errors. Scanning or reading equipment manufacturers would benefit by knowing how to develop or program their equipment more effectively and efficiently (based on the bar codes or identifiers used by manufacturers and accepted by hospitals). Parties could also agree to encode information that we do not require as part of the bar code, such as lot number and expiration date information, and could agree on the automatic identifier(s) for encoding that information and the equipment for reading or interpreting the encoded information. If parties could develop consensus mechanisms that enjoy widespread or unanimous support among those who would apply, use, and develop automatic identification technologies, then we could possibly reduce our involvement.

We disagree, however, with the comment's claim that the rule creates ''enormous uncertainty'' for hospitals. The linear bar code establishes a minimum, technological ''floor'' that hospitals will be able to rely upon when deciding on equipment purchases. Although the comment is correct that we will not object if firms encode lot number and expiration date information voluntarily, we reiterate that the inclusion of such information is voluntary, and so we will not dictate how such voluntarily-provided information is presented. Moreover, creating a ''sunset'' date as the comment suggested could increase the possibility that hospitals will not invest in equipment until the sunset date is reached. Hospitals might decide to defer their investments because, when the sunset date arrives, drug manufacturers could decide to switch to two-dimensional symbologies, thereby making one-dimensional scanners either obsolete or in need of upgrades. So, under a ''sunset'' scenario, hospitals could decide to wait until after the sunset date to see whether manufacturers, repackers, relabelers, and private label distributors agree on a particular technology, and this would reduce the rule's benefits.

(Comment 62) One comment said we should review the bar code requirements on a regular basis to determine whether they are preventing or reducing medication errors.

(Response) We intend to monitor medication error reports and published literature to assess the rule's impact on medication error rates. As more drugs are bar coded and as more hospitals become capable of scanning and interpreting those bar codes, we will be interested to hear from hospitals about their experiences using bar coded drugs and the impact on medication errors.

4. Miscellaneous Comments

(Comment 63) One comment said that scanning devices must be ergonomically designed and the labels must be small enough to fit on drug products. The comment added that scanners must be able to read labels that are on curved surfaces.

(Response) Issues concerning scanner design and capability are outside the scope of this rule. Given the abundance and variety of scanners (i.e., whether the scanner is ''tethered'' to another device or ''wireless'' or whether the scanner is ''heavy duty'' to withstand impact in case it is dropped), we believe that hospitals should be free to choose the scanners or reading equipment that is best suited to their needs.

Similarly, issues concerning label size are outside the scope of this rule.

However, with respect to reading bar codes on drug labels, the bar code's ''readability'' would be subject to GMPs, and, under 21 CFR 211.122, any labeling material (which would include the product label) that does not meet appropriate written specifications ''shall be rejected to prevent their use in operations for which they are unsuitable.''

(Comment 64) One comment said that the rule could advance other public health objectives or issues, such as product traceability, authentication, counterfeiting, and terrorism. It said we should not ignore such issues during the rulemaking process.

(Response) We know that various public health initiatives might benefit from technological solutions. However, consideration of other public health initiatives should occur in a different forum where all interested parties have the opportunity to consider the initiative or issue and explore options (see, e.g., 68 FR 52773, September 5, 2003) (announcing a public meeting on FDA's efforts to combat counterfeit drugs)). It would be inappropriate for this final rule to invoke other reasons for a bar code requirement when the administrative record has focused almost exclusively on the need to prevent or reduce medication errors.

(Comment 65) One comment said that the rule could have a negative impact on hospital pharmacies if the bar code technology does not recognize generic drug products. The comment also stated that, if a pharmacy stocks one brand, and then stocks a different brand the next week, drugs from both brands might still be located in automated dispensing machines; in such a scenario, the comment asked how bar coding would work.

(Response) The comment may have misunderstood the rule. Regarding generic drug products, the final rule requires the bar code to contain the drug's NDC number. Generic drug products have their own NDC numbers that are distinct from those used by other manufacturers. Thus, there should be no technological barrier to using the

bar code to identify generic drug products.

As for automated dispensing machines, this rule is neither intended nor designed to assist in inventory control matters. Thus, a hospital pharmacy that mixes drugs from different sources in its automated dispensing machines (and presumably removes those drugs from their packages and accompanying labels) may not be able to use bar code technology to differentiate between different drugs inside the automated dispensing machine.

(Comment 66) One comment said we should address the subject of prescribers' handwriting because misread or illegible handwriting may lead to medication errors. It added that we should address drug names that sound alike and copies of ''NCR paper'' that are difficult to read. The comment did not explain what it meant by NCR paper or why copies of such paper are difficult to read.

(Response) Issues regarding handwriting and paper quality are outside the scope of this rule and may also be outside our jurisdiction.

(Comment 67) One comment said we should do ''whatever it takes'' to decrease medication errors and increase the productivity of nursing staff. Another comment said that nurses need a trustworthy, correct, and speedy system that reduces workload and is more efficient than manual systems. It urged that nursing staff be involved and adequately trained in bar coding processes.

(Response) The final rule should help detect potential medication errors before they can result in harm to patients and, as a result, decrease medication errors. However, insofar as nursing staff productivity is concerned, we believe that there may be an initial small productivity loss due to the use of new technology (see 68 FR 12500 at 12527), but that, overall, the rule's benefits greatly exceed productivity loss.

As for involving nursing staff in bar code systems development and training, such matters are outside the scope of this rule and may also be outside our jurisdiction.

(Comment 68) One comment said that the pharmaceutical industry could support the necessary hardware and software to maintain databases on drug sample use and to alert pharmaceutical manufacturers when drug inventories are low. The comment suggested other data uses and database possibilities, such as making data available for physicians and the pharmaceutical industry (but protecting patients' identities) and having FDA control or regulate large databases on drug use and drug safety.

(Response) Issues concerning the creation, financing, and maintenance of databases are outside the scope of this rule. Aside from our MedWatch program, we have no plans to control or regulate large databases on drug use and drug safety.

(Comment 69) One comment said we should cover ''non-standard'' items at minimal cost to the pharmacy. The comment listed ointments, lipids, crash cart supplies, and total parenteral nutrition as examples of ''non-standard'' items, but it did not explain why such products needed bar codes.

(Response) We decline to revise the rule as suggested by the comment. Requiring bar codes on prescription drugs, OTC drugs that are commonly used in hospitals and dispensed pursuant to an order, blood, and blood components will cover the majority of products that could present a risk of medication error. Thus, to the extent that any of the comment's ''non-standard'' items are prescription drugs or OTC drugs that are commonly used in hospitals and dispensed pursuant to an order, they would be subject to the bar code requirement unless otherwise exempted.

As for a product's cost to pharmacies, we do not regulate the costs that firms may charge to pharmacies. Thus, product cost issues are beyond the scope of this rule, although we consider the rule's economic impacts in section VII of this document.

(Comment 70) One comment asked for our guidance regarding scanners on certain intravenous infusion pump systems. The comment said that two manufacturers have infusion pump systems that are equipped with scanners, but the scanners only read bar codes used by the same manufacturer. The comment said that this practice forces hospitals to buy drugs from the same manufacturer who made the infusion pump system and creates a financial hardship on hospitals. The comment acknowledged that hospitals can relabel drugs themselves, but said that hospital relabeling would eliminate the rule's benefits.

(Response) Issues concerning scanner capabilities in existing infusion pump systems are outside the scope of this rule. However, as we stated in our response to comment 41, the bar code's ability to affect medication error rates depends largely on the ability of hospitals to scan and interpret the data in the bar code. So, for example, choosing a commonly-used linear bar code symbology in a standard that scanners can easily read will have a greater impact on patient safety compared to a unique bar code symbology that few (if any) scanners are programmed to read.

I. How Will We Implement the Rule?

The preamble to the proposed rule suggested that we would give affected parties 3 years to comply with the bar code requirement for human prescription drugs and OTC drugs commonly used in hospitals and dispensed pursuant to an order (see 68 FR 12500 at 12512). It suggested a similar implementation period for blood and blood components (see 68 FR 12500 at 12514). The preamble to the proposed rule also invited comment on whether the implementation period should be shortened (see 68 FR 12500 at 12529, question 9).

(Comment 71) Many comments said that a 3-year implementation period is sufficient or acceptable, although some expressed a desire to have the final rule effective at the earliest possible date. One comment agreed that a 3-year implementation period is sufficient, but cautioned that packaging issues could complicate implementation.

In contrast, many other comments advocated a shorter implementation period. These comments recommended different implementation periods, such as:

- 2004 or December 31, 2004. Several comments sought implementation by 2004 because they believed that manufacturers, repackers, relabelers, and private label distributors could comply earlier or because, in one case, the entity submitting the comment explained that its contracts with drug suppliers require bar codes at the unit-of-use package level by 2004.
- 2 years. One comment noted that some drug manufacturers are already placing bar codes on their products, so the comment felt the industry could meet a 2-year implementation period. Another comment, from a drug manufacturer, endorsed a 2-year implementation period because the rule only required the NDC number to be encoded in the bar code. A different comment said that manufacturers should obtain FDA approval of label changes (due to the bar code) within 2 years, but added that the implementation period could be reduced to 18 months if manufacturers supported such a reduction.
- a tiered implementation strategy whereby drugs that we approve after the final rule's effective date must comply with a bar code requirement at an earlier time. Five comments suggested a 2-month period for drugs approved after the final rule's effective date, and some

comments suggested that drugs approved before the final rule's effective date should have no more than 3 years to comply.

One comment requested that we shorten the implementation period without specifying a different implementation period.

One comment declared that shortening the implementation period would be useless because hospitals would not be ready to use bar codes and because manufacturers have not analyzed possible changes to the NDC number.

One comment asked whether products that are already on the market without a bar code can remain on the market through their expiration date.

Only one comment advocated a longer implementation period. The comment said the implementation period should be 5 years if we refuse to create a general exemptions provision. The comment stated that the additional time would allow for further development of new technologies to address space limitations on small products.

(Response) We have decided to amend the implementation scheme as follows. First, for drugs that are approved on or after the effective date of this rule, we would expect compliance within 60 days after the drug's approval date. Early implementation of a bar code requirement for newly-approved drugs is appropriate because such drugs will not present the same label redesign issues as previously-approved drugs.

Additionally, early implementation of a bar code requirement for newly-approved drugs will create an incentive for all parties to develop and use bar codes, and this should have a beneficial impact on patient safety.

Second, for drugs approved before the effective date of this rule, we would expect compliance within 2 years after that date. We agree with the comments that companies have already demonstrated their ability to put bar codes on their drug products quickly and agree that requiring only the NDC number in the bar code should facilitate implementation. A 2-year implementation period will also enable firms to exhaust existing stock. If a drug has an expiration date that exceeds 2 years, and the drug was not subject to the bar code requirement at the time it was marketed, we will allow that drug to remain on the market without a bar code.

However, we recognize that we cannot preclude the possibility that some drug products may be difficult to bar code, either because of their containers, size, or other complications. Therefore, if a manufacturer, repacker, relabeler, or private label distributor can demonstrate to us that, for technological reasons, it cannot comply within 2 years after the final rule's effective date, it should contact us. If we agree that the firm cannot comply within 2 years, we may give the firm an additional year to comply with the rule. We will not entertain any requests for additional time based on non-technological considerations; for example, if a firm is unable to decide on which linear bar code symbologies to use, that indecision would not justify an additional year to comply with the rule. As another example, if a firm decided to encode more information (other than the NDC number) voluntarily, but was experiencing difficulties encoding that additional information, we would not agree to an additional year to comply with the rule.

Firms who believe that technological reasons prevent them from complying within 2 years of the rule's effective date should contact the center responsible for their particular product. For human drug products, the contact office is the Office of New Drugs Compliance (HFD–020), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

For biological products, including blood and blood components, the contact office is the Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852.

As for those comments that would defer implementation until any regulatory changes to the NDC number occur or would seek a 5-year implementation period if we refuse to create a general exemption provision, we decline to adopt their suggestions. Because we have not yet issued a drug establishment registration and listing proposal (which would include provisions regarding possible regulatory changes to the NDC number), we cannot predict how the NDC number will change or whether it will change at all. We can predict that the NDC numbers for drugs approved after the final rule's effective date should be unique (because we have devoted more attention to NDC numbers recently to ensure that they are unique), will remain unchanged even if we revise the NDC number system, and will be capable of being encoded in bar codes.

Additionally, we decline to extend the implementation period to 5 years to allow for possible technological developments for small products. As we noted in our response to comment 27, firms have placed linear bar codes on products as small as 1 mL vials, and the UCC itself stated that no pharmaceutical member to the UCC had presented a case of a product that was too small to bear an RSS bar code. Thus, existing bar code symbologies may be satisfactory for small packages. We also remind parties that there may be other options, such as changing packaging, to accommodate the bar code.

(Comment 72) One comment focused on blood and blood components. The comment said the implementation period should be 1 year. The comment explained that ISBT 128 has been approved by CBER and the American Association of Blood Banks (AABB) since 2000 and that a 1988 AABB implementation task force had recommended an 18-month implementation plan.

(Response) For uniformity among products we believe that a 2-year implementation period is appropriate for human drug products, biological products, and blood and blood components. Blood banks are, of course, free to implement the requirements of the rule on a shorter time schedule.

(Comment 73) One comment asked if we could offer any incentives to manufacturers to get them to comply quickly with a bar code requirement.

(Response) We have given manufacturers, repackers, relabelers, and private label distributors considerable flexibility in selecting their own linear bar code symbologies, their data standards (i.e., EAN.UCC or HIBCC), and the bar code's placement on the label. We have even simplified, to the maximum extent we can, the manner in which manufacturers, repackers, relabelers, and private label distributors would report their bar code label changes to us (i.e., through annual reports rather than supplements that require our approval). These efforts should minimize the regulatory burden on manufacturers (and others who are subject to the bar code requirements) and make it easier for them to comply with the rule at the earliest opportunity.

III. Legal Authority

We believe we have the authority to impose a bar coding requirement for the efficient enforcement of various sections of the act. These include sections 201(n), 201(p), 501, 502, 503, 505, and 701(a)) of the act (21 U.S.C. 321(n), 321(p), 351, 352, 353, 355, and 371(a)), and sections 351 and 361 of the PHS Act (21 U.S.C. 262 and 264).

A bar coding requirement for drugs, including biological products, would permit the efficient enforcement of the

misbranding provisions in section 502(a) and (f) of the act, as well as the safety and effectiveness provisions of sections 201(p) and 505 of the act. Bar coding is expected to significantly advance: (1) The provision of adequate directions for use to persons prescribing, dispensing, and administering the drug; (2) the provision of adequate warnings against use by patients where a drug's use may be dangerous to health; and (3) the prevention of unsafe use of prescription drugs.

Section 502(a) of the act prohibits false or misleading labeling of drugs. This prohibition includes, under section 201(n) of the act, failure to reveal material facts relating to potential consequences under customary conditions of use. Information in a database that could be readily accessed through the use of a bar code, such as the drug's strength, dosage form, route of administration, and active ingredient and drug interactions is material with respect to consequences which might result from use of the drug under such conditions of use. Because all of the drugs (prescription drugs and the subset of covered OTC drugs) covered by this final rule may be used in the hospital setting, such use in hospitals can be considered the ''conditions of use as are customary or usual.'' Bar coding can be expected to reduce the incidence of the following types of medication errors:

- Administering the wrong dose to a patient;
- administering a drug to a patient who is known to be allergic;
- administering the wrong drug to a patient or administering a drug to the wrong patient;
- administering the drug incorrectly;
- administering the drug at the wrong time; and
- missing or duplicating doses.

Because information accessed through use of the bar code will reveal material facts relating to potential consequences under customary conditions of use, the bar code requirements are justified under section 502(a) of the act.

Section 502(f) of the act requires drug labeling to have adequate directions for use, adequate warnings against use of a drug product by patients where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration, in such manner and form, as necessary to protect users. The bar code would make it easier for the person administering the drug to have full access to all of the drug's labeling information, including directions for use, warnings, and contraindications. Moreover, because the bar code's information would go to the computer where it could be compared against the patient's drug regimen and medical record, the person administering the drug will be able to determine whether the right patient is receiving the right drug (including the right dose of that drug in the right route of administration) at the right time. The person administering the drug will also be able to avoid giving products to a patient who might be allergic to, or otherwise unable to take, a particular drug. Because the bar code will facilitate access to information including adequate directions for use and adequate warnings, the bar code requirements are justified under section 502(f) of the act.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the act, we will approve a new drug application (NDA) only if the drug is shown to be safe and effective for its intended use under the conditions set forth in the drug's labeling. Bar coding would allow health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is given to the right patient at the right time. Thus, bar coding will ensure the safe and effective use of drugs by reducing the number of medication errors in hospitals and other health care settings.

Section 505(b)(1)(D) of the act requires an NDA to contain a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug. The same requirement exists for abbreviated new drug applications (see section 505(j)(2)(A)(vi) of the act) and for biological products (see 351(a)(2)(B)(i)(II) of the PHS Act). Information in the bar code would reflect the facilities and controls used to manufacture the product. As described in section II.C.1 of the preamble, the NDC number would identify the manufacturer, product, and package.

A bar coding requirement also would permit the efficient enforcement of the adulteration provisions of the act. A regulation requiring the bar coding of products should avert unintentional mix up and mislabeling of drugs during labeling, packaging, relabeling, and repacking. A bar coding requirement therefore helps prevent adulteration under section 501(a)(2)(B) of the act. It is a manufacturing method or control necessary to ensure that a drug product has the identity and strength its labeling represents it to have, and meets the quality and purity characteristics which the drug purports or is represented to possess.

Requiring that the bar code be surrounded by sufficient blank space, and remain intact under normal conditions of use, would also further the efficient enforcement of section 502(c) of the act. Section 502(c) of the act provides that a drug product is misbranded if: any word, statement, or other information required by or under authority of the act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use. The requirement that the bar code be surrounded by sufficient blank space and remain intact under normal conditions of use would help ensure that the bar code can be read easily and accurately so that its safety benefits may be realized.

Because licensed biological products, including blood, are also prescription drug products, the sections of the act discussed elsewhere in the legal authority section provide ample legal authority for issuance of this regulation. However, 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 bar code requirement for biological drugs, and the machine-readable information requirement for blood and blood components, are designed to ensure the continued safe and effective use of licensed biological products. Thus, we may refuse to approve biologics license applications (BLAs), or may revoke already approved licenses, for biological products or blood and blood components that do not have such codes or information.

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 requirement for machine-readable information will aid in the control of units that are at risk of spreading communicable diseases.

After the effective date of any final rule, if a product required by the final rule to bear a bar code does not have such a bar code, the product may be considered adulterated or misbranded under the act and would be subject to

regulatory action. Our enforcement actions under the act include, but are not limited to, seizure, injunction, and prosecution, and violation may result in withdrawal of approval of a product's marketing application.

IV. Environmental Impact

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

V. Paperwork Reduction Act of 1995

A. What Is the Estimated Information Collection Burden?

This final rule contains information collection requirements that are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). We describe the provisions below in this section of the document with an estimate of the annual reporting burden. Our estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Bar Code Label Requirement for Human Drug and Biological Products

Description: We are issuing a new rule that would require human drug product and biological product labels to have bar codes. The rule requires bar codes on most human prescription drug products and on OTC drug products that are dispensed pursuant to an order and commonly used in health care facilities. The rule also requires machine-readable information on blood and blood components. For human prescription drug products and OTC drug products that are dispensed pursuant to an order and commonly used in health care facilities, the bar code would contain the NDC number for the product. For blood and blood components, the rule specifies the minimum contents of the machine-readable information in a format approved by the CBER Director as blood centers have generally agreed upon the information to be encoded on the label. The rule will help reduce the number of medication errors in hospitals and other health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being given to the right patient at the right time.

Because bar code information for drugs subject to an NDA or ANDA will be reported through an annual report, this rule affects the reporting burden associated with 21 CFR 314.81(b)(2)(iii). Section 314.81(b)(2)(iii) requires the submission of an annual report containing a representative sample of package labels and a summary of labeling changes (or, if no changes have been made, a statement to that effect) since the previous report. Here, the bar code would result in a labeling change. We have previously estimated the reporting burden for submitting labels as currently required under § 314.81(b)(2)(iii), and OMB has approved the collection of information until March 31, 2005, under OMB control number 0910–0001. We are not re-estimating these approved burdens in this rulemaking; we are only estimating the additional reporting burdens associated with the submission of label changes under § 314.81(b)(2)(iii).

Minor label changes for blood and blood components may be reported as part of an annual report, as described in 21 CFR 601.12(f)(3), and we would consider the machine-readable information on blood and blood component labels to be a minor change. We have previously estimated the reporting burden for submitting labels as currently required under § 601.12(f)(3), and OMB has approved the collection of information until August 31, 2005, under OMB control number 0910–0338. We are not re-estimating these approved burdens in this rulemaking; we are only estimating the additional reporting burdens associated with the submission of label changes under § 601.12(f)(3).

Parties may also seek an exemption from the bar code requirement under certain, limited circumstances. Section 201.25(d) requires submission of a written request for an exemption and describes the contents of such requests.

Description of Respondents: Manufacturers, repackers, relabelers, and private label distributors of prescription drug products, including biological products, or OTC drugs that are dispensed pursuant to an order and commonly used in hospitals.

We estimate the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency of Responses	Total Annual Responses	Hours per Response	Total Hours
201.25 and 610.67	1,447	31.1	45,000	24 hours	1,080,000
§ 201.25(d)	40	1	40	24 hours	960
314.81(b)(2)(iii)	1,447	5.9	8,576	10.5 minutes	1,497
601.12(f)(3)	211	1	211	1 minute	3.5
606.121(c)(13)	981	42,507.7	41.7 million	1 minute	695,000
Total					1,777,550.5

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Our estimates are based on the following assumptions:

• For prescription drugs whose label changes would be reported in an annual report pursuant to § 314.81 or § 601.12(f)(3) for biological products), there are approximately 1,447 registered establishments that would be reporting. Information on listed drugs indicates there are 89,800 separate, identifiable product packages that will comply with the bar code requirement. These packages account for 8,576 separate and distinct products (each product is marketed in an average of 10.47 packaging variations). This means that the annual frequency of reports would be 5.9 (8,576 products subject to annual

reports/1,453 registered establishments = 5.92 products per registered establishment, which we have rounded down to 5.9). Section 314.81(b)(2)(iii) requires firms to submit an annual report that includes a summary of any changes in labeling since the last annual report. Similarly, § 601.12(f)(3)(i)(A) requires manufacturers of biologics to include in their annual reports editorial or similar minor labeling changes. We expect that the addition of a bar code to a label would necessitate a simple statement in the annual report declaring that the bar code has been added, so we have assigned an estimate of one minute for such statements per label. Each product's annual report would include labels for all packaging variations. Thus, the total reporting burden would be 1,496.67 hours ((8,576 reports x 10.47 labels (or one label per packaging variation) per report x 1 minute per report)/60 minutes per hour = 1,496.67 hours), which we have rounded up to 1,497 hours.

• For minor labeling changes for blood and blood components included in an annual report under § 601.12(f)(3)(i)(A), FDA's database indicates there are 211 licensed manufacturers of transfusable blood and blood components. We expect that the addition of machine-readable information to the label of blood and blood components would necessitate a simple statement in the annual report declaring that the machine-readable information has been added, so we have assigned an estimate of one minute for such statements. Thus, the total reporting burden would be 3.5 hours ((211 reports x 1 minute per report)/60 minutes per hour = 3.516 hours), which we have rounded down to 3.5 hours.

• For the requirement in § 601.121(c)(13) to include machine-readable information on blood and blood components, FDA's registration database indicates there are 981 blood and plasma establishments. The AABB estimates that approximately 13.9 million blood donations are collected annually. We estimate that each blood donation yields approximately three blood components. This means that the frequency of responses is approximately 41.7 million occurrences (13.9 million blood donations x 3 blood components per donation) divided by 981 establishments or 42,507.645 occurrences per establishment, which we have rounded up to 42,507.7. We estimate that it takes one minute to apply a machine-readable code manually; if a blood collection facility uses an on-demand printer, the time would range between 15–30 seconds. For purposes of this estimate, we adopt the larger time estimate of one minute per machine-readable information for blood, thus resulting in an annual reporting burden of 695,000 hours ((41.7 million reports x 1 minute per report) /60 minutes per hour = 695,000 hours). However, we reiterate that facilities using on-demand printers would face lower burdens. In addition, blood collection centers are currently allowed and encouraged to apply machine-readable information to collections. This burden estimate accounts for requiring an activity that is currently voluntary and does not reflect an additional activity.

• For exemption requests under § 201.25(d), we believe that few products would warrant an exemption from the bar code requirement. Consequently, based on our experience with other exemption provisions, we estimate that there may be 40 exemption requests per year and that each exemption request will require 24 hours to complete. This should result in an annual reporting burden of 960 hours (40 requests per year x 24 hours per request = 960 hours).

B. What Comments Did We Receive on Our Estimates?

Several comments disagreed with our estimates, and one comment even disagreed that the rule would have practical utility insofar as its products were concerned.

(Comment 74) Specifically, two comments from allergenic extract firms disagreed with our claim that reporting label changes would take only 1 minute. One comment claimed that the estimate would be 400 hours for its firm, based on 15 minutes per label report and 30 product labels per report. It declared the burden to be ''onerous and unnecessary.'' The comment declared that the rule would not enhance our oversight of the allergenic extract industry and would not reduce medication errors because allergenic extracts are administered in physician's offices and clinics where ''mistakes do not normally occur.'' The second comment stated that its firm would have to submit label changes for 1,200 labels and 1,200 packages at 10 minutes per report, for a total burden of over 400 hours, and declared this would be an ''unnecessary hardship'' on a small firm.

(Response) The final rule exempts allergenic extracts from the bar code requirement, so the comments' claims are moot. However, we reiterate that we expect that the addition of a bar code to a label would necessitate only a simple statement in the annual report, which is already a required document (see 68 FR 12516; 21 CFR 314.81). This statement would simply declare that the bar code has been added to the label. So, for example, if the statement in the annual report was, ''We added a bar code to the label pursuant to 21 CFR 201.25,'' it is difficult to see why such a statement requires 10 or 15 minutes to prepare or insert into an annual report, and even more difficult to see why such a statement results in a 400-hour burden for a firm. The comments did not explain how it arrived at its estimate of 10 and 15 minutes per report, so, because we have no basis to evaluate the accuracy of the comments' larger time estimates, we decline to adopt them.

(Comment 75) One comment from a medical gas firm said that we underestimated the number of firms subject to the rule. The comment said that there are over 3,000 medical gas sites alone.

(Response) Our estimate was based on the number of firms that have registered with FDA, and one should remember that the final rule applies to manufacturers, repackers, relabelers, and private label distributors who are subject to the drug establishment registration requirements (see § 201.25(a)). We do not know whether the comment's claim of over 3,000 medical gas ''sites'' includes firms that are not subject to our drug establishment registration requirements, but if a firm is not subject to the drug establishment registration requirement, then it would not be subject to the bar code requirement.

Yet, even if we were to accept the comment's estimate of 3,000 medical gas establishments and assumed that all were subject to the drug establishment registration requirements, we do not need to change our Paperwork Reduction Act estimates because the final rule exempts medical gases from the bar code requirement.

The information collection provisions in this final rule have been approved byOMB. (OMB control number: 0910–0537; expiration date 2/28/07).

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VI. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various

levels of government. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Analysis of Impacts

A. Introduction

We have examined the rule under Executive Order 12866, the Regulatory Flexibility Act as amended by the Small Business Regulatory Enforcement Fairness Act, the Unfunded Mandates Reform Act, and the Congressional Review Act. Executive Order 12866 directs 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, distributive impacts and equity). 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. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any regulation that may result in expenditure by State, local, and tribal governments, or by the private sector of $100 million in any one year (adjusted annually for inflation). Currently, such a statement is required if costs exceed about $110 million for any one year. The Congressional Review Act requires that regulations determined to be major must be submitted to Congress before taking effect.

The regulation is consistent with the principles set forth in Executive Order 12866 and the three statutes. We have identified the regulation as an economically significant regulatory action, as defined in Executive Order 12866. We believe the regulation is unlikely to have a significant impact on a substantial number of small entities. The expected impact of this regulation is greater than $110 million in a single year and therefore is considered a major regulatory action as defined by the Unfunded Mandates Reform Act. The Office of Information and Regulatory Affairs (OIRA) in the Office of Management and Budget (OMB) has determined this regulation to be major under the Congressional Review Act.

We estimate that the rule provides net benefits to society of $3.4 billion to $3.6 billion annually, depending on whether a discount rate of 3 percent or 7 percent is used. This estimate relies on work by the Eastern Research Group, Inc. (ERG), which we contracted to collect data, interview industry experts, and analyze the costs and benefits of the rule. The detailed analysis and references in support of the impacts summarized in Table 2 is included in the docket as Reference 46 and is available on FDA's Web site. In section VII.O below, we present our analysis of the substantial uncertainty in the estimates presented in Table 2.

TABLE 2.—ESTIMATED IMPACTS OF THE FINAL RULE IN MILLIONS OF DOLLARS ANNUALIZED OVER 20 YEARS

Discount Rate	Regulatory Costs	Anticipated Hospital Costs*	Societal Benefits**	Net Benefits (benefits minus costs)	Potential Hospital Efficiencies***
7 Percent	$8	$660	$5,200	$4,500	$380 to $600
3 Percent	$7	$600	$4,900	$4,300	$360 to $570

Note: These estimates may not sum because of rounding.
*Costs due to voluntary accelerated purchase and utilization of bar coding systems
**Benefits to public health due to avoidance of adverse drug events
***Potential additional benefits from efficiencies in reports, records, inventory, and other hospital activities.

Table 2 presents the total expected regulatory costs to manufacturers, repackers, relabelers, retail outlets, and FDA. Most of these costs will occur during the first several years after implementation. Table 2 also shows the estimated opportunity costs of the expected accelerated investment in bar coding systems by the hospitals. These investment expenditures are necessary to achieve the societal benefits expected from the rule. Table 2 also shows our estimated range of possible efficiencies in hospital activities associated with accelerated adoption of technology. Both anticipated hospital costs and the societal benefits would occur after hospitals purchase and install the necessary equipment to take advantage of bar codes. The net benefit of the rule is the societal benefit minus the induced expenditures minus the regulatory costs. The net benefits of the rule, which are $3.6 billion and $3.4 billion per year if annualized at 7 percent and at 3 percent, are $38 billion and $51 billion in present value terms, if calculated at 7 percent and 3 percent discount rates respectively. These estimates, however, account for neither expected potential hospital efficiencies, nor income transfers following fewer awards for medical malpractice.

While efficiency gains in hospital recordkeeping and reporting procedures produce societal benefits, we are extremely uncertain that hospitals would make the additional investments to achieve them. This final rule focuses on the use of bar code technology only in hospital pharmacies and patient care wards. Such systems could provide the opportunity and incentive for hospitals to expand bar code technology into other areas of operation, such as billing or supply ordering. The installation of bedside systems may make such an expansion more likely, but we believe it would not be a direct effect of this final rule. In addition, the estimated efficiency gains are extremely uncertain. However, we have noted the potential of these additional gains, but have not claimed them as direct benefits of this final rule.

We also note that reductions in income transfers from the potential reduction in medical malpractice awards and reductions in medical liability insurance that may occur with reductions in adverse drug events are not considered societal benefits because they do not represent resource or opportunity savings. These effects are discussed later in this section, but do not contribute to the estimated net benefits shown in Table 3.

B. Objective of the Rule

The objective of the rule is to enable the health care sector to utilize technological solutions to reduce preventable adverse drug events (ADEs)[1] and acute hemolytic

[1] For this analysis an adverse drug event (ADE) is an injury from a medicine (or a lack of an intended medicine) (source: American Society of

Continued

transfusion reactions (AHTRs) associated with medication errors[2] and transfusion errors in hospitals.[3]

C. Estimate of Preventable Adverse Drug Events and Acute Hemolytic Transfusion Reactions

In 1999, the Institute of Medicine (IOM) issued a report that drew public attention to the number of deaths that occur each year in the United States from preventable medication errors in hospitals. A significant proportion of the reported deaths, as well as the additional illnesses and morbidities, were associated with errors involving FDA-regulated products, especially medications. This section briefly describes our efforts to estimate the current number of preventable ADEs and AHTRs.

The public health literature includes many attempts to determine the rate of preventable ADEs in United States hospitals, although these studies typically employed varying methodologies and definitions. Our methodology begins by multiplying estimated hospital admissions by reported rates of ADEs per admission. We combined the resulting number of ADEs per hospital per year with the reported ratio of preventable to total ADEs to estimate the number of preventable ADEs per hospital per year. We first developed these calculations for various hospital size classes and then aggregated the data to present national estimates. We relied on published literature to derive ADE rates for each major stage of the medication process in hospitals. We then projected preventable ADEs for the entire evaluation period based on expected future increases in hospital admissions.

We used a similar methodology to estimate preventable AHTRs.

ERG identified four comparable published studies that reported rates of ADEs per hospital admissions (Refs. 2 to 5). The reported incidence rates of hospital admissions with ADEs ranged from 2.4 percent to 6.5 percent with a mean rate of 4.3 percent. According to AHRQ, there were 29.1 million non-obstetric hospital admissions during 2000 [4]. We multiplied these admissions by 0.043 and found that approximately 1.25 million ADEs occur annually in United States hospitals. The same four studies reported that between 15 percent and 49 percent of all ADEs are preventable. We used the mean of these studies to estimate that about 373,000 (30 percent) of these ADEs were preventable. Based on published reports (Refs. 2 and 6), we also estimated that 1,048,000 potential ADEs[5] are either intercepted before reaching the patient or do not cause an injury. According to projected increases in hospital expenditures and population demographics that imply future increases in hospital admissions, the annual number of preventable ADEs would total 478,000 within 20 years.

ERG searched the public health literature to identify stages in the hospital medication process in which errors occur and concluded that the medication stages of prescribing, transcribing, dispensing, and administration provide a useful analytic structure. The most common reported ADE symptom was cardiac arrhythmia followed by itching and/or nausea. Relatively few fatalities have been documented as preventable ADEs, but several published studies conclude that 2.8 percent of all preventable ADEs probably result in fatalities. Another study has asserted that as many as 2.7 percent of all ''negligent'' (as defined in the study) ADEs resulted in permanent disability. We used these estimates in our analysis.

AHTRs resulting from erroneous blood transfusions have been extensively studied and widely reported. Based on data provided by the National Blood Data Resource Center (NBDRC), ERG estimated that United States hospitals currently transfuse approximately 15.7 million units of whole blood and red blood cells to 5.2 million patients per year. According to recent studies (Ref. 27) the frequency of erroneous ABO-incompatible transfusion errors is approximately 1 per 38,000, or 414 errors per year. Another study (Ref. 7) has estimated that two-thirds of all incompatible transfusions were the result of preventable errors. Using this figure, the current number of annual preventable erroneous blood transfusions that result in AHTRs is 276. In addition, the literature reports that potential blood transfusions that could have resulted in adverse outcomes but did not account have a frequency five times actual errors (Ref. 8). Thus, we have estimated 276 preventable and 1,380 potential AHTRs occur in hospitals each year. The NBDRC has estimated an annual growth rate of transfusions of 6 percent. Discussions with hospital personnel believe this may be an overestimate, so we have used a 3 percent annual growth in transfusions to forecast preventable AHTRs over time. Therefore, within 20 years we expect 498 preventable and 2,492 potential AHTRs in the absence of this regulation.

D. The Final Rule

With certain exceptions, we are requiring linear bar codes on almost all prescription drug and biological products (including vaccines) and all over-the-counter (OTC) drug products commonly used in hospitals and dispensed pursuant to an order. We are also requiring the use of machine-readable information on all human blood and blood components intended for transfusion. For drug products, this information will include National Drug Code (NDC) number identifying the dosage, strength, nature, and form of each administered product and be portrayed in a linear bar code[6] and include product-specific and package-specific NDC numbers. We will maintain a database of all unique NDC numbers and ensure these data are available for use in commercial computerized systems that can provide bedside bar code identification. The bar code requirement would be effective within 2 years. For blood and blood components, the machine-readable information will include information identifying the facility, the lot number relating to the donor, a product code, blood type, and Rh.

We are issuing this rule because private markets have failed to establish the standardized bar codes that are needed to motivate hospitals to adopt an important health-saving technology. In particular, we believe that the private market's failure to develop standardized bar codes has impeded the growth of the technological investment necessary to

Hospital Pharmacists, 1998). The definition used for the analysis in the proposed rule included AHTRs, which are shown separately for the final rule's analysis.

[2] For this analysis a medication error is a preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (source: NCCMERP, 2002).

[3] For this analysis a hospital is a facility that provides medical, diagnostic and treatment services that include physician, nursing and other health services to inpatients and the specialized accommodation services required by inpatients (source: NAICS, 2002). We have excluded psychiatric, alcohol and chemical dependency, rehabilitation, and other specialty hospitals. We have included general medical and surgical hospitals in which the average stay is less than 30 days.

[4] Obstetric admissions are rarely associated with ADEs. The referenced articles have eliminated these admissions in their analyses. Reasons for the low probability of ADEs include the relatively healthy state of most admissions as well as the low number of medications.

[5] A potential ADE is a medication error that could have caused an ADE, but did not. Potential ADEs include medication errors that were intercepted before reaching the patient. Potential ADEs include any errors that do not involve patients.

[6] A bar code is a graphic representation, in the form of bars and spaces of varying width of numeric or alphanumeric data.

reduce the number of ADEs and AHTRs in the nation's hospitals. We find that a regulatory intervention to establish a standardized system of bar codes is needed to address this market failure.

The final rule will increase costs to the manufacturers, repackers, relabelers, and private label distributors of the affected products by requiring changes in manufacturing, packaging, and labeling processes. It will also increase costs to some hospitals by requiring a change in some bar code readers associated with these products. The final rule will also require FDA resources to ensure industry compliance with the bar coding requirement and additional resources to maintain a computerized database of NDC numbers. Once bar codes are standardized, the final rule will enable hospitals to take advantage of the coded information that would permit hospitals to reduce ADEs, while achieving other operational cost efficiencies. The final rule will also enable other sectors to use machine-readable technology in ways that would benefit public health (for example, accessing up to date labeling information from home computers or identifying drugs subject to recalls).

E. Description of Affected Sectors

1. Current Machine-Readable Technologies

Prior to developing the rule, we contracted with ERG to examine the current machine-readable technologies available for use by the health care sector and report on trends. The resulting report is included in the docket (Ref. 9), and summarized here.

Bar coding is currently the most widely used machine-readable technology and is also the technology most likely to see increased acceptance in the near future. Health care companies have sponsored two organizations that have each developed different bar code symbologies;[7] the Uniform Code Council's Universal Product Code (UPC) and the Health Industry Business Communication Council's Health Industry Bar Code (HIBCC). UPC codes are more widely used in retail stores while HIBCC is specially designed to safeguard against errors. However, although HIBCC codes have been effectively used in the medical device industry, they have not won wide acceptance within pharmaceutical markets. Within these symbologies, the groups have defined acceptable linear (or one-dimensional) codes, two-dimensional codes, and composite codes (a combination of one- and two-dimensional symbologies). The advantage of two-dimensional and composite codes is that they can include additional information in the same area. Potential disadvantages of two-dimensional and composite symbologies are the higher costs for readers and scanners and the additional risk of uncertain data recovery by misinterpreting coded information.

While these organizations' bar codes are widely used, their use for the prevention of ADEs remains limited. Most pharmaceutical and OTC manufacturers use bar codes to move shipping cases through their distribution chain, but relatively few pharmaceuticals are sold with the specific bar codes required by this rule. Some hospitals use computer-controlled technology to add their own bar codes to incoming products.

Bar code systems require printers, scanners, and software to ensure that correct information is communicated. According to discussions with consultants, pharmaceutical manufacturers prefer to label products as late as possible in the manufacturing process in order to maximize flexibility. Printing technology advancements have allowed more printing options to be available. Manufacturers currently use contract label printers or packagers along with in-house operations. Contract printers are commonly used for preprinted labels that do not carry customized data. Currently, ink jet and thermal printers may be appropriate for production line printing of bar codes, although ink jet printers may cause difficulties in media compatibility, print speed, and resolution. Water-based inks can streak or blur, but non-water soluble inks produce a shine that reflects to the scanner and affects how the bar code is read. Laser printers are subject to toner flaking, which makes them unreliable for long-term bar code printing. Production line speeds may also create problems for bar code resolution levels.

The complexities of bar code scanners have evolved as the codes have become more data intensive. Most scanners in current use are laser-based systems designed to read linear bar codes. In health care settings, scanners are routinely programmed to discriminate among the symbologies they are likely to encounter. Some laser scanners can also read composite or two-dimensional codes, if properly programmed. These scanners are more costly, and some consultants have cautioned that multiple data systems may introduce potential misreading at hospital bedsides. Moreover, in certain situations, health care scanners may not need to use all of the available information. For example, scanners at bedside point of care may only need to capture limited identifying information while the central dispensing pharmacies may require full database capabilities. At this time, the scanning industry is confident that linear standards[8] will be readily accessible, whereas other standards may require additional market research. We believe that scanners will work in conjunction with hand-held personal digital assistants (PDAs) in hospital wards due to their portability and multi-functional characteristics.

2. Manufacturers and Packagers of Affected Products

A large majority of exterior pharmaceutical packages already include the NDC number in a bar code, according to discussions with staff at two large Veteran Health Administration Comprehensive Mail Order Pharmacies. The final rule, however, by requiring this bar coded information on the drug's label, may result in a bar code on both exterior and interior packaging. In addition, some prescription and OTC drug products are already sold in blister packs, where individual pills or capsules are enclosed in a bubble. Prescription products are often repackaged into blister cards for more convenient use in hospitals. While some blister cards may now be labeled with bar codes for specified concerns, many are not. OTC drug products in blister packs rarely have bar coded information. Moreover, many bar coded exterior packages cannot be read by hospital or retail scanners, because manufacturers use bar codes for sales promotions and other special offers that have separate and distinct NDC numbers that do not appear in all customer databases.

There are currently about 1,218 establishments in the Pharmaceutical and Biologic Preparation industries (NAICS 325412 and 325414). Based on the size distribution of industry establishments, we estimate a total of about 3,513 in-house packaging production lines. In addition, an estimated 229 establishments in the Packaging and Labeling Services industry (NAICS 561910) are dedicated to serving the pharmaceutical industry, accounting for an additional 482 packaging lines. Overall, we estimate that 3,995 packaging lines are used in 1,447 establishments for these products.

In addition, we estimate there are 981 blood collection centers in the United States (NAICS 621991). Each of these collection centers acts as a separate

[7] A symbology refers to a distinct technological, machine-readable language.

[8] A standard refers to a general description of a system of machine-readable languages.

packaging line. Consultants have estimated that about 25 percent of these blood collection centers are included in published industry counts. We added blood collection centers to the industry packaging lines for a total of 4,976 affected packaging lines in 2,428 separate establishments.

The number of separate trade and generic named affected products is about 17,000, an increase greater than 500 percent since 1990. Each of these named products may be marketed in varying strengths or dosage forms. Using data from the current NDC number list, we have estimated there are 78,000 separate prescription unit-of-sale packages, 98,000 OTC drug packages, and 2,000 blood/vaccine packages. Over time, the number of distinct packaging units is expected to continue to increase. The OTC drug industry has suggested that as many as 10 percent of OTC packages (9,800 packages) are commonly used in hospital settings and would be subject to the bar code rule. For example, OTC analgesics that may be dispensed to a patient pursuant to an order would be subject to the final rule, but shampoos or toothpastes that may be provided would not. The Consumer Healthcare Products Association (CHPA) estimated that as many as 10 percent of their member's products were regularly dispensed from hospital pharmacies or packaged specifically for sale to hospitals. Other responses include a report from a hospital that only 200 OTC products are routinely dispensed. However, discussions with OTC manufacturers and hospital pharmacists have indicated larger potential coverage. Hospital pharmacists periodically order wide arrays of products from catalogs. While some categories of OTC products are unlikely to be affected by the regulation, ERG has estimated that as many as 75 percent of OTC shelf-keeping units (SKUs) could potentially be used in hospitals and subject to the requirement of this regulation. For purposes of this analysis, because we do not know the specific SKUs that will be ''commonly used in hospitals,'' we have assumed that 75 percent of all OTC drug products (73,500 SKUs) would be required to provide bar coded information. Overall, 153,500 separate unit-of-sale packages are expected to be subject to the final rule.

OTC drug manufacturers frequently redesign labels. Based on discussions with manufacturers, the majority of OTC labels are redesigned within a 6-year cycle for marketing reasons. Many products have redesigned labels every 2 or 3 years. Prescription drug product labels may be redesigned less frequently, but there is evidence that numerous labeling changes occur. We examined selected NDA files and found that changes to prescription drug product labels occur, on average, more than once per year. While marketing of prescription drug products may not be as sensitive to labeling graphics and package design as OTC products, there are many other reasons why manufacturers change their product labels. For this analysis, we have nevertheless assumed that the final rule will result in significant involuntary relabeling by the industry.

3. Retail Outlets

Retail pharmacies currently have the capability to read linear standardized bar codes at their in-house scanners. According to the National Association of Chain Drug Stores, there are 55,000 community and chain pharmacies (NAICS 446110), and pharmacies in supermarkets and mass merchandisers (NAICS 445110) that utilize over 515,000 scanners. The expected useful life of a retail scanner is 5 years.

The current stock of scanners in retail outlets may require upgrades or replacement if the bar code rule were to mandate reduced space symbology (RSS). These upgrades would not be a direct requirement of the alternative, but would have been necessary for these entities to continue with bar coded activity. The retail sector currently relies on UPC or other symbologies and adopting such a standard would not require scanner replacements or upgrades. The final rule covers only those OTC drug products commonly used in hospitals and dispensed pursuant to an order. Although small vials or bottles may require specific RSS symbology, these items are available to consumers in larger packages that accommodate current standards for retail outlets. The regulation is not expected to impact this sector, but, in developing this rule, we have considered alternatives that would affect retail outlets.

4. Hospitals

The final rule does not require hospitals to introduce the new automated technologies, but the development of consistent bar codes on drugs and consistent machine-readable information on blood and blood components will greatly encourage hospitals to implement bar code based systems to reduce ADEs associated with medication errors. Moreover, unit-dose blister packs and other vials and small bottles would probably need bar codes using the RSS symbology. In order to properly scan these products, hospitals that currently have installed bar code readers would have to upgrade or replace some scanners. According data from the National Center for Health Statistics (NCHS), there are 5,040 hospitals in the United States (NAICS 622) with a total of about 850,000 beds that will be likely to use bar code technology. Estimates of personnel in these hospitals include 48,500 pharmacists, 44,500 pharmacy assistants, and almost 1.2 million nurses. Overall, a nurse is responsible for 3 beds per shift. An average hospital includes 170 beds and employs about 10 pharmacists, 9 pharmacy assistants, and 237 nurses.

Hospitals are currently adopting bar code technology to better control the entire medication process and improve the delivery of care to patients. Virtually all hospital pharmacies use bar code scanners for inventory and stock keeping activities, but only approximately 1 percent of all hospitals have installed bedside, point-of-care systems that use bar coded information. An additional 3 percent of hospitals use some form of computerized system in the medication process, but not all use bar codes. Overall, an estimated 2 percent of all hospitals (101 hospitals) currently use bar codes in everyday operations. Even in the absence of the regulation, we expect the remaining 4,939 hospitals to gradually implement computerized tracking systems. Discussions with industry consultants and the American Hospital Association (AHA), however, suggest that without standardization, hospitals would need an estimated 20 years to adopt and use systems with bar code readers and to use in-house overpackaging and self-generation of bar code identifiers. ERG discussed with several consultants whether 20 years is a realistic horizon for acceptance of this technology. While they recognized the uncertainty of future projections in this area, industry experts felt that 20 years was not an unreasonable expectation. We examined the impact of alternative future acceptance rates as a sensitivity analysis.

We requested comments on the potential uses of bar code information on drug products at a public meeting held on July 26, 2002. Comments from that public meeting indicated that while patient safety reasons were the primary goals for installation of scanning systems, there are other potential uses. Industry groups and individual hospitals noted that installation of scanning systems may lead to more efficient inventory control, purchasing and supply utilization, and other potential risk management activities.

Other groups noted that an integrated computerized network would assist billing and laboratory systems as well. The AHA stated that bar codes would improve patient care and safety, increase workforce productivity and satisfaction, streamline payment, billing, and administrative systems, lead to efficient management of assets and resources, and meet consumer expectations for service and access to information. We believe these comments indicate that internal investment decisions concerning the acquisition of computerized systems entail additional returns that are in addition to ADE and AHTR avoidance. While some of these returns to hospitals (such as reduced liability awards and malpractice liability insurance premiums) may be partly transfers, we believe such additional efficiencies are likely.

5. Nursing Homes and Long-Term Care Facilities

We analyzed the potential impact of bar code technology for the prevention of preventable ADEs in nursing homes and other long-term care facilities (NAICS 623110). According to the American Health Care Association (AHCA), there are 16,456 nursing homes in the United States, 11 percent of which are hospital-based. These facilities account for about 1.8 million beds with an occupancy rate of over 85 percent. The AHCA estimates there are 561.7 million patient-days in nursing homes each year, with 1.5 million annual admissions. Most nursing homes are serviced by long-term care (LTC) pharmacies. There are approximately 3,000 of these pharmacies, including those that only service nursing homes.

6. FDA Oversight and Responsibilities

We would be affected in three areas. For successful bar code use, hospitals need access to the unique NDC numbers that identify specific active ingredients, packages, dosage forms, and units. We would maintain the database containing these unique identifiers and arrange access to it for the private sector.

We would also develop and maintain a process of reviewing and granting exemptions to these regulatory requirements for specific products. Although we estimate that we will receive approximately 40 annual exemption requests, we cannot accurately predict the resources required to process these exemption requests.

The third area in which our activities would be impacted by the final rule would be our use of compliance resources. The final rule requires affected products to have bar coded information (or machine-readable information in the case of blood and blood components). Although the exact impact on our compliance resources is not quantified, we recognize that the creation of new regulatory requirements will need additional resources to ensure compliance.

F. Regulatory Costs of the Final Rule

1. Introduction

We estimated costs for a 20-year evaluation period to reflect the time that hospitals would take to invest in bar code technology in the absence of the regulation. This summary describes these costs and presents both the present value (PV) and the annualized value of the cost streams. We analyzed costs to the affected sectors over the entire evaluation period using both 7 percent and 3 percent annual discount rates. We assume that costs and expenditures accrue at the beginning of each year. The detailed calculations and references that support the following analysis are available as Reference 1.

2. Costs to Manufacturers and Packagers of Affected Products

The pharmaceutical industry would face compliance costs from this regulation, because we would require manufacturers, repackers, relabelers, and private label distributors to include NDC numbers in bar code format, using linear bar code symbology for all unit of dosing products. The final rule requires this information within 2 years of the implementation date. The final rule also affects the production processes of the pharmaceutical and biological product industries. Although manufacturers appear to initiate labeling changes fairly often for internal purposes, the final rule could lead to large-scale production line alterations that could affect a manufacturer's entire product line.

a. *Prescription drugs.* Based on ERG's analysis, we expect the overall investment costs to the prescription drug industry to total $28.1 million over the first 2 years of the evaluation period. Among the major components of these investment costs are $17.4 million resulting from modifications of unit-dose interior packaging to include a unique NDC number in a linear bar code format for every product. Exterior packaging modifications that include NDC information would cost $6.1 million over the 2-year period. Because the capital equipment installed for these packaging modifications would require upgrading and replacement after an average 10 years of productive life, the industry would invest an additional $4.7 million over the 11th and 12th evaluation years for this replacement and upgrade. In addition, the packaging production process would result in additional annual operating and maintenance costs reaching $0.4 million by the second evaluation year. In total, we estimate that the costs incurred by the prescription drug manufacturers, repackers, and relabelers to comply with the final rule over the 20-year period would be $3.2 million per year if annualized using a 7 percent annual discount rate, and $2.5 million if annualized using a 3 percent discount rate.

b. *Over-the-Counter drugs.* The OTC drug industry has estimated that fewer than 10 percent of their products are commonly used in hospitals (CHPA, 2002). However, suppliers and hospitals have asserted that as many as 75 percent of OTC SKUs would at least occasionally be ordered for hospitals. For this analysis, we assume that 75 percent of all OTC drug products could be required by the rule to include bar coded NDC numbers. It is likely the industry would either assign internal production processes that could allow labeling differentiation for these products, or repackers and relabelers would provide the required labeling. We believe that the packaging changes required to install bar coding equipment are so large they would result in manufacturer decisions to bar code entire product lines rather than incremental, specific products. We estimate that the initial investment for OTC drug manufacturers, repackers, and relabelers would total $19.9 million over 2 years, with additional capital investments of $1.5 million during the 11th and 12th evaluation years. The estimated annual operating costs to provide bar codes to the affected proportion of the OTC drug market are expected to reach $0.3 million by the second year. Overall, the estimated annualized costs to the OTC drug industry, using a 7 percent annual discount rate over the 20-year evaluation period, are $2.2 million. With a 3 percent annual discount rate, the annualized costs to OTC manufacturing firms are $1.6 million.

c. *Blood and blood components intended for transfusion.* Manufacturers of blood and blood components intended for transfusion could also be minimally affected by the rule, but we could not identify a manufacturer of blood and blood components intended for transfusion that does not currently apply bar coded information that includes information required by this final rule. The final rule does not specify a particular bar code standard

for this market segment. Therefore, we do not believe this final rule will pose any incremental costs to this industry.

d. *Total cost to manufactures, repackers, relabelers, and private label distributors.* The annualized costs to manufacturers, repackers, relabelers, and private label distributors of prescription products, OTC products, and human blood and blood components are $5.4 million using a 7 percent discount rate. Using a 3 percent discount rate, the annualized costs to manufacturers, repackers, relabelers, and private label distributors are $4.1 million.

3. Costs to Retailers and Distributors

We do not expect increased costs to retailers, wholesalers, and distributors. Currently installed scanners and readers are able to read the proposed linear standard bar codes. However, if we issued an alternative regulation requiring specific RSS symbology, independent community pharmacies, chain pharmacies, and pharmacies in chain merchandisers or supermarkets would have had to upgrade scanners in order to take advantage of the proposed standardized information. Given the widespread reliance on bar code information in the retail sector, the currently installed stock of bar code scanners will not be affected by the rule.

4. Costs to Hospitals

The final rule requires NDC numbers in linear bar codes on the labels of the affected products. However, because we expect that manufacturers, repackers, relabelers, and private label distributors may find it necessary to use RSS symbology on small unit-dose packages or vials and bottles, hospital scanners and readers must have the ability to capture this information in RSS format. As a result, in order for hospitals with currently installed bar code reading systems to maintain current operating practice, some scanners must be replaced with scanners that are RSS-capable. Replacement of these scanners is necessary to maintain current operations.

These costs are somewhat mitigated for the approximately 2 percent of all hospitals (101 hospitals) that currently utilize bar codes in everyday practice by repackaging medications in unit-dose form and applying internally printed and generated bar codes. According to published reports and discussions with industry experts, ERG estimated that such hospitals now incur costs to repackage and apply bar codes to about 95percent of dispensed medications. These 101 hospitals would avoid some of these expenditures (because 25 percent of all medications will have useable bar codes) under the rule.

The final rule would result in the premature replacement of scanners used in hospital pharmacies and treatment wards. ERG has estimated that the annualized, incremental costs to hospitals of accelerating scanner replacement or upgrades to read RSS symbology is $0.8 million (at a 7 percent discount rate) or $0.6 million (at a 3 percent discount rate).

According to literature reports, it costs as much as $0.03 per unit-dose to apply a bar code in hospital pharmacies. Currently, 25 percent of dispensed medication must have bar codes applied by in-house pharmacy in unit-of-use packages. Avoidance of this activity under the final rule will reduce costs by about $0.2 million per year.

Overall, we estimate the average annualized costs of the final rule less the cost savings to hospitals to be $0.6 million using a 7 percent annual discount rate and $0.4 million using a 3 percent annual discount rate.

5. Costs to the Food and Drug Administration

According to a recent study, the number of available pharmaceutical products has increased by 500 percent in 10 years and now totals over 17,000 separate trade and generic names. With the multitude of dose strengths and packages, the total number of unique packaging units is now 178,000 separate identifiable products. Of this total, we expect 153,500 of these packaging units to require bar coded NDC numbers because we estimate that 75 percent of all OTC drug products will be affected. Even if the recent growth rate in new products were halved (so that the number of available products increased by 500 percent in 20 years), there would be 890,000 new NDC codes over 20 years, or 44,500 per year for the evaluation period.

We expect that the requirement for notification of unique NDC numbers would require the development and maintenance of an accessible agency database. We have assumed 0.5 hours per notification to represent the cost to input and encode a specific NDC number and to maintain an accessible database containing all NDC numbers. This implies an annual resource requirement of 22,250 hours, or approximately 10 full-time equivalents (FTEs). These direct resources require supervision, administration, and support. To account for these indirect resources, we multiplied direct resources by 2, resulting in 20 annual FTEs. The most recent FDA budget documents have used a value of approximately $120,000 per FTE. Therefore, we expect the annual costs of maintaining a system of unique NDC numbers to be $2.4 million. Although additional regulatory requirements, such as developing and operating a exemption waiver process or requiring readable bar code information on product labels, would increase our administrative and compliance burdens, we have not quantified these impacts.

6. Total Regulatory Costs

The total direct annualized regulatory costs of the final regulation over the 20-year period amounts to $8.4 million using a 7 percent annual discount rate and $6.9 million using a 3 percent discount rate. These costs differ from the costs estimated for the proposed rule because of our analyses of the proportion of affected OTC drug products, the human blood and blood component industry, hospital responses to bar codes, and a 2-year implementation period. Table 3 shows future projections for the increased investments and operating and maintenance costs expected from the regulation.

TABLE 3.—REGULATORY COSTS BY YEAR IN MILLIONS

Evaluation Year	Investment During Year	Operating and Maintenance Cost
1	$32.6	$2.6
2	$24.0	$2.9
3	0	$2.9
4	0	$2.9

TABLE 3.—REGULATORY COSTS BY YEAR IN MILLIONS—Continued

Evaluation Year	Investment During Year	Operating and Maintenance Cost
5	0	$2.9
6	0	$2.9
7	0	$2.9
8	0	$2.9
9	0	$2.9
10	0	$2.9
11	$3.2	$2.9
12	$3.0	$2.9
13	0	$2.9
14	0	$2.9
15	0	$2.9
16	0	$2.9
17	0	$2.9
18	0	$2.9
19	0	$2.9
20	0	$2.9

G. Other Anticipated Expenditures

We anticipate that the final rule will affect facilities defined as hospitals and included in the NCHS report on Health 2002.[9] The final rule would impact hospitals (NAICS 622) by encouraging them to accelerate the efficient use of bar code reading technology in bedside point of care settings. The expected increased investment would lead to a significant reduction in the number of ADEs and AHTRs among hospital patients. We assume that hospital investments in this technology occur at the beginning of each year.

Hospitals have long considered the application of bar code reading technology for their facilities. According to the American Hospital Association (AHA), almost half of United States hospitals have explored the possibility of independently installing this technology. A few (about 4 percent of all United States hospitals) are currently using some form of computerized systems in their medication processes, and half of them use bar codes in everyday practice. However, because hospitals currently have no standardized bar coded information for all therapeutic products, each hospital must generate and internally affix bar codes that are applicable only within that specific facility. In some cases, hospitals overpackage drug products in order to make current scanning systems usable. This extra effort reduces the expected efficiency of the bar code reading systems, introduces potential errors, and has been a barrier to the general acceptance of readable technology. Standardized universal codes would remove this impediment and encourage health care facilities to invest and use technology to reduce patient ADEs and AHTRs.

Hospital facilities will face significant capital investments and significant process changes in order to implement bar code reading and scanning technology. ERG estimated that the average initial cost to a typical hospital for the installation of scanners, readers, software, initial training etc. is $448,000.[10] In addition, although there is considerable uncertainty, hospital industry executives and consultants contacted by ERG agree that negative productivity effects are likely after installation of a bar code reading system. These contacts noted that using scanners could result in reductions in patient ward productivity because current scanners and administration procedures would have to be revised to accommodate the technology. Difficulties could arise, for example, when multiple doses of medication are required at the same time for different patients; or when current administrative practices, such as pre-preparing certain medication, could not be accommodated with the bar code reading systems. Also, moving the scanner and reader from room to room, not adequately reading the bar code on one swipe, and other procedural changes might result in operational inefficiencies. It is possible (and hopeful) that long-term process changes would moderate or eliminate these potential inefficiencies. While some consultants believed that bar code systems would ultimately be resource neutral, the most detailed analysis of the VA system (Ref. 10) estimated a 10 percent loss of nursing productivity after implementing a bar code system. Our analysis assumes that hospital ward productivity levels would fall by 3 percent annually over the evaluation period. We examine the effects of alternative assumptions in section VII.O below. The annual opportunity costs of these productivity losses, together with the operation and maintenance expenses, amount to $556,000 per year for the average sized hospital. (Operating costs are slightly higher if installed systems are unable to take advantage of required bar codes on labels). Some of these expected productivity losses would be mitigated by efficiency gains in other hospital procedures as discussed later.

Despite these costs, interviews with consultants in the field of health care technology indicate that hospitals are gradually making this commitment. Experts have predicted that even in the absence of this regulation, hospitals would likely install bar code readable technology within 20 years. Therefore, we believe that while only about 101 hospitals currently use bar codes in everyday operations, the remaining 4,939 hospitals would ultimately invest in this technology. These experts have also predicted, however, that if standardized bar code information on medications were available to allow scanning systems to capture information without requiring in-facility labeling systems, many hospitals would be swayed to make these investments much earlier. Thus, we believe that the regulation would effectively prompt facilities to accelerate these investments.

Based on ERG's discussions with industry consultants, we predict that the rule could double the rate of hospital investment in this technology, thereby achieving the installation of complete systems within 10 years. For example, for those hospitals that now expect to acquire bar code systems within 10 years, we assume the availability of standardized bar codes on medications would accelerate the purchase to within 5 years. The cost to the hospital of this accelerated investment expenditure is the opportunity cost of the investment capital for 5 years (the difference between making the investment in year 5 as opposed to year 10) as well as the 5 additional years of maintenance expenses and productivity losses. In addition, industry experts suggest that systems of bar code readers and scanners would require software and equipment upgrades within 10 years of installation. For the example facility, the installed system would require upgrades during the 15th project year under the accelerated investment, whereas upgrades would not occur until the 20th year in the absence of regulation. We acknowledge that precise estimates of the rate of acceleration of technology acceptance are uncertain. However, industry experts indicated that doubling the rate of technology acceptance was not an unreasonable assumption. Alternative rates of acceptance were compared and discussed as a sensitivity analysis.

ERG used a probit pattern of adopting bar code reading technology. That is, the percentage of hospitals adopting the technology is modeled as a standard normal cumulative distribution with 0 percent adoption in year 0 and 100 percent adoption in year 20. The standard deviation of the distribution is chosen to ensure at least 1 adoption during the first year. This function has been used to describe rates of technology acceptance for other new products. In the hospital sector, for example, a study of medical technology infusion noted that complete unit dose systems, complete IV (intravenous) admixture systems, and computerized prescribed order entry (CPOE) systems have been accepted in this manner (Ref. 11). Consequently, for the 20-year period, FDA estimates the PV of the costs of the accelerated investment in bar coding technology by hospitals, including the annual operating expenses and productivity losses, to be $7.0 billion (7 percent) or $9.0 billion (3 percent). The estimated annualized cost is $657.2 million (7 percent) or $602.9 million (3 percent). As discussed in

[9] We have tried to quantify impacts on nursing and residential care facilities (NAICS 623) in response to comments on the proposed rule, but the relatively high costs of installing integrated bar code scanning systems and the relatively low rate of reported ADEs make it unlikely that the rule will affect this sector.

[10] Per hospital expenditures and benefits are based on an average sized hospital based on bed capacity. The average United States hospital has 170 beds (NCHS, 2002).

section VII.F.4, the regulation would reduce hospital operating costs because pharmacies would not apply in-house bar codes. In baseline, hospitals installing bar code systems would incur these expenses. Therefore, we expect that by the 17th year, annual operating costs for this industry will be lower than those that would occur in the absence of the regulation. Table 4 shows the annual incremental expenditures for adopting hospitals expected under the final regulation.

TABLE 4.—EXPECTED INCREMENTAL HOSPITAL EXPENDITURES BY YEAR IN MILLIONS

Evaluation Year	Incremental Cost to Hospitals Adopting Bar Codes
1	$0.8
2	$13.5
3	$102.8
4	$426.8
5	$1,039.3
6	$1,624.0
7	$1,852.3
8	$1,751.9
9	$1,478.0
10	$1,129.6
11	$772.4
12	$466.6
13	$243.0
14	$104.9
15	$32.6
16	$0.5
17	($11.6)
18	($17.0)
19	($17.5)
20	($17.7)

( ) indicates cost reduction from baseline to account for decreased in-house packaging.

H. Reduction in Preventable Adverse Drug Events and Preventable Acute Hemolytic Transfusion Reactions

The benefits of the rule are focused on the reductions in ADEs and AHTRs that would follow the earlier use of bar code reading technology and bar coded drug products. We have not quantified all the other institutional benefits of computerized systems and medical informatics, but have estimated a potential range of efficiency gains. Any ADEs avoided during a year are analyzed as if they occur at the end of the year.

ERG determined that under current conditions, about 1.25 million ADEs occur each year in the United States, of which 373,000 are preventable. As discussed above, the regulation would substantially reduce the number of ADEs caused by errors originating in the dispensing and administration of pharmaceutical or blood products in hospitals. Studies of medication errors in hospitals that have installed bedside bar coding and use internally applied labels show error interception rates of from 70 percent to 85 percent (Refs. 12 to 15 and 28). Other industry experts, however, suggest that those published interception rates would not be as high if the technology were widely dispersed, because of the likelihood of events such as lost wristbands, erroneous bar codes, or intentional system bypasses. Therefore, FDA and ERG have assumed that bar code system use would produce no reduction in prescribing and transcribing errors, but that its use would intercept one-half of the 45.1 percent of all preventable ADEs that now originate in the dispensing and administration stages of the medication process. Thus, ERG assumed that, if all hospitals adopted bar code systems, the number of preventable ADEs would fall by 22.6 percent (45.1 x 0.5), which would currently prevent about 84,300 ADEs per year (373,000 x 0.226). This equals a reduction of 16.7 preventable ADEs per year for an average hospital. Section VII.O below addresses the effect of alternative assumptions. Given projected increases in hospital admissions, within 20 years, we expect 543,000 preventable ADEs in the absence of this regulation. This analysis suggests that this regulation would prevent 123,000 ADEs, or 24.5 per hospital during the 20th evaluation year. We believe the assumption that bar code readers could intercept one-half of dispensing and administration errors is reasonable and conservative, but specifically tested this assumption as a sensitivity analysis.

Errors occur during any of the numerous steps in the production and delivery of blood and blood components. Several studies (Refs. 8, 16, and 27) have estimated that approximately 55 percent of transfusion errors occur in patient areas and originate from phlebotomy errors or incorrect patient identification. The machine readable information required on human blood products will be readable by installed systems. We expect bedside bar code systems to intercept 75 percent of these errors based on published case studies of interception rates that vary between 50 and 100 percent. Therefore, installation of bar code systems in hospitals is expected to prevent 114 AHTRs (276 x 0.55 x 0.75), or 0.023 per hospital. During the 20th evaluation year, bar code systems are expected to prevent 206 AHTRs (0.041 per hospital).

We estimate that the final rule, by stimulating earlier hospital investment in bar code scanning systems, will reduce ADEs and AHTRs. To project the aggregate number of ADEs and AHTRs avoided due to the final rule, ERG calculated the number of ADEs and AHTRs per hospital that would be avoided by bar coding systems and multiplied that number by the additional number of hospitals that would use bar coding reading systems during each year of the evaluation period. For example, during the 10th evaluation year, our model predicts that 2,469 more hospitals would have installed bar code reading systems than would have installed them in the absence of the rule. The additional hospitals using bar codes during the 10th year would intercept an estimated 52,600 errors, taking into account expected increases in admissions as well (21.3 ADEs per hospital x 2,469 hospitals), that would otherwise have resulted in ADEs during that year. In addition, there would be 75 fewer AHTRs because of the increased use of bar code systems during that year. Over the entire evaluation period, this methodology predicts that the accelerated investment would avoid over 501,300 ADEs and 700 AHTRs.

I. Value of Avoided ADEs and AHTRs

1. Value of Avoided ADEs

Estimating benefits requires estimating the value of the avoided ADEs and AHTRs. FDA and ERG estimated two values of avoided preventable ADEs. First, ERG estimated the avoided direct hospital costs needed to cover additional tests, longer patient stays, and other direct expenses. Based on published studies, the estimated average direct cost of an ADE not attributable to prescribing error is $2,257 (Refs. 3, 5 and 29). This figure represents a weighted average of direct hospital costs over all degrees of ADE severity and does not include patient pain and suffering or liability. Second, ERG and FDA estimated the monetized value of avoiding decreases in quality-adjusted life years (QALYs) due to ADEs. This latter approach attempts to value a patient's subjective ADE experience, including inconvenience,

pain and suffering, foregone earnings, and other out-of-pocket costs.

ERG examined the literature to determine the probability distribution of specific symptoms associated with ADEs. These reported symptoms range from rashes and itching to cardiac arrhythmia, renal failure, and mortality. The duration of each symptom (additional length of hospital stays) ranged from about 0.7 days to 5.5 days (except for mortality). ERG then examined reported preference scores from the Harvard Center for Risk Analysis' (HCRA) Catalog of Preference Scores, which includes a survey of the health economics literature and presents published estimates of preferences for defined symptoms. The preference scores ranged from 0.95 (for significant but not serious ADEs) to 0.00 for death. Typical symptoms encountered with serious ADEs had a preference score of 0.8, while life-threatening ADEs had a derived preference score of 0.6. We note that the reported preference scores vary widely by definition and methodology and must be interpreted with great caution.

ERG calculated the change in QALYs expected from an avoided ADE as 1 minus the preference score multiplied by the duration of the event. For example, minor drug toxicity (such as a rash) has a derived preference score of 0.95 and a reported duration of 2 days (0.005 years). The change in QALYs expected for such an event is 0.05 (1 minus 0.95) x 0.005, or 0.0003 QALYs. There is no consensus on the best means of valuing QALYs or the best estimates of willingness-to-pay for QALYs. One approach is to derive the value from studies that estimate the willingness-to-pay to avoid a statistical mortality risk. For example, values derived from occupational wage-premiums to accept measurable work-place risk are about $2 million to $10 million per statistical death avoided, with a typical estimate of about $5 million. Apportioning this value over the remaining life expectancy of the average workforce member and adjusting for future disability implies (at 7 percent discount rate) a value per QALY of about $373,000. If using a 3 percent discount rate, the adjusted value per QALY is estimated at about $213,000. Thus, in the example above, the value of the decrease in QALYs due to minor drug toxicity would be $102 (7 percent) or $64 (3 percent).

ERG examined the literature and found that by combining several published accounts, 36.1 percent of the outcomes associated with preventable ADEs were deemed significant, 41.7 percent were deemed serious, 19.4 percent were deemed life threatening (of which 10 percent [or 1.9 percent of the total] resulted in permanent conditions), and 2.8 percent resulted in fatalities. Overall, these assumptions indicate that the weighted average preference value for each avoided preventable ADE is $183,500 with a 7 percent annual discount rate. A 3 percent annual discount rate would indicate a weighted average preference value of $181,600. The derived values are similar because the contribution of avoided mortality. We note that these values are very sensitive to the number of fatal preventable ADEs.

2. Value of Avoided AHTRs

As for ADEs, AHTRs caused by erroneous transfusions might lead to additional laboratory tests, extended hospital stays, and other direct costs. ERG judged that these direct additional hospital costs would be equivalent to those for ADEs and estimated them to equal $2,257 per AHTR.

To estimate the monetary value of a change in QALYs resulting from erroneous transfusions, ERG examined the range of potential reactions experienced by patients that receive ABO-incompatible blood. As reported in two studies (Refs. 7 and 27), almost half (47 percent) of patients suffer no ill effects, and 3 percent of patients may die due to an underlying condition. Most of the remaining half of patients may experience fever, chills, chest pain, nausea or other relatively mild symptoms for short durations. However, an AHTR may occasionally lead to acute renal failure or death. The weighted average preference value for each avoided AHTR is $101,200 using either 7 percent or 3 percent discount rate. As for ADEs, this estimate is dominated by the high value placed on mortality avoidance.

J. Aggregate Benefit of Avoiding ADEs and AHTRs

FDA and ERG estimated the benefit of avoiding ADEs and AHTRs due to the use of bar code reading systems by multiplying the value of each avoided preventable ADE and AHTR by the expected number of ADEs and AHTRs avoided. As stated earlier, an average hospital is expected to have fewer preventable ADEs and fewer preventable AHTRs each year under current conditions after installing bar code reading technology. Within 20 years, these systems are expected to avoid 24.5 ADEs and 0.041 AHTRs per hospital because of increased admissions. The direct cost savings by avoiding treatment ($2,257 per ADE or AHTR) and the weighted preference values ($183,500 per ADE and $101,200 per AHTR) indicate a societal value of $185,800 per average ADE avoided and $103,500 per average AHTR avoided (using 7 percent discount rate), and a societal benefit of about $3.48 million per facility during the first evaluation year. We multiplied this derived value per hospital by the expected difference in the number of hospitals with installed bar code technology under the rule. For example, during the 10th evaluation year, an estimated 2,469 additional hospitals would have installed bar code reading systems due to the rule. We would expect the increased use of these systems to result in 51,500 fewer ADEs and 71 fewer AHTRs than in the absence of the regulation. The estimated PV of avoiding these ADEs and AHTRs during the 10th year is $4.9 billion (7 percent) or $7.1 billion (3 percent). The PV of the societal benefits that would result from reductions in ADEs and AHTRs over the entire 20-year evaluation period is $54.8 billion (7 percent). The annualized societal benefit of the reduced number of ADEs and AHTRs is $5.2 billion at 7 percent annual discount rate. Table 5 illustrates the expected reduction in ADEs and AHTRs for the entire evaluation period. The PV for AHTR avoidance alone is $42.2 million and annualized at $4.0 million at 7 percent.

TABLE 5.—EXPECTED REDUCTION IN ADES AND AHTRS BY YEAR WITH BAR CODE SOCIETAL BENEFITS IN MILLIONS (7 PERCENT)

Evaluation Year	Additional ADEs Avoided	Additional AHTRS Avoided	Gain in QALYS	Monetized Benefit of Avoided ADEs/AHTRs
1	37	0	57.7	$6.8
2	595	1	928.4	$110.6

TABLE 5.—EXPECTED REDUCTION IN ADES AND AHTRS BY YEAR WITH BAR CODE SOCIETAL BENEFITS IN MILLIONS (7 PERCENT)—Continued

Evaluation Year	Additional ADEs Avoided	Additional AHTRS Avoided	Gain in QALYS	Monetized Benefit of Avoided ADEs/AHTRs
3	4,566	6	7,129.2	$849.2
4	18,171	25	28,369.0	$3,378.8
5	46,364	64	72,384.5	$8,621.1
6	72,898	101	113,808.7	$13,554.8
7	83,230	115	129,938.8	$15,476.0
8	79,083	110	123,464.9	$14,704.9
9	66,933	93	104,495.8	$12,445.7
10	51,528	71	80,445.8	$9,581.3
11	35,521	49	55,455.9	$6,604.9
12	21,828	30	34,078.4	$4,058.8
13	11,732	16	18,316.0	$2,181.5
14	5,493	8	8,575.2	$1,021.3
15	2,232	3	3,484.2	$414.9
16	774	1	1,208.6	$143.9
17	239	0	373.5	$44.4
18	58	0	90.3	$10.7
19	12	0	18.3	$2.2
20	0	0	0	$0
Total	501,294	693	782,623.2	$93,211.8

Using a 3 percent discount rate, the PV of avoided ADEs and AHTRs totals $73.0 billion with an average annualized equivalent of $4.9 billion. The benefit attributable to avoided AHTRs alone has a PV of $56.8 million and an annualized value of $3.8 million using 3 percent annual discount rate.

K. Cost Effectiveness of Bar Coding

In order to estimate the value of each ADE or AHTR avoided, ERG estimated the decrease in QALYs that would be expected from each event. As discussed in section VII.I.1, each ADE or AHTR avoided represents a weighted average of potential outcomes. The weighted average decrease in QALYs for an ADE was 1.56 QALYs and 0.87 for each AHTR. These estimates imply that each avoided ADE would contribute 1.56 QALYs to the public. As shown in Table 5, over the entire course of the evaluation period, the number of avoided ADEs and AHTRs account for 782,623.2 QALYs gained. The PV of these QALYs gained equals 460,508 using a 7 percent discount rate and 618,861 using a 3 percent discount rate.

Table 6 shows the cost-effectiveness per QALY gained at various discount rates. The costs used to estimate the effectiveness include the direct regulatory costs as well as increased expenditures by hospitals. Cost-effectiveness shows that the regulation will require costs of between $9,000 and $15,000 for each additional QALY gained.

TABLE 6.—COST EFFECTIVENESS PER QALY GAINED

	Cost-Effectiveness at 7 percent	Cost-Effectiveness at 3 percent
Undiscounted QALYs	$9,009	$11,595
QALYs Discounted at 7 percent	$15,311	N/A
QALYs Discounted at 3 percent	N/A	$14,663

Note: Present value of costs are divided by the gain in QALYs. For example, the present value of costs using a 7 percent discount rate is approximately $7.05 billion. This amount, when divided by approximately 782,600 QALYs, results in $9,009 per QALY ($9,008.43, rounded up to $9,009).

L. Other Benefits of Bar Code Technology

The availability of standardized bar codes would result in additional benefits to patients and the health care sector. As bar codes are an enabling technology, their adoption for hospital patient care would foster their use in other hospital and non-hospital settings. With automated systems, hospitals would no longer need to repackage and self-generate bar codes. Hospital pharmacies and wards would likewise take advantage of the availability of bar coded products to generate new production efficiencies for activities such as reporting, record keeping, purchasing, and inventory controls. For example, integrated scanning systems may allow for electronic versions of daily Medication Administration Records (MARs) and pharmacy reconciliation reports. According to industry experts, if these activities could be avoided by automatically generating the records, an average sized hospital could save as many as 397 hours of pharmacist resources and 5,694 hours of nursing resources each year. The estimated annual efficiency savings of avoiding these opportunity costs equals $218,300 for an average hospital. Moreover, ERG and FDA believe the identified potential gains from electronic MAR and reconciliation reports may account for only between 50 and 80 percent of the potential gains in these areas. Discussions with several hospital administrators indicate that integrated bar code systems could result in reduced ''hallway'' time and improved communication. For example, nurses will spend less time walking between a patient and the nursing station to resolve discrepancies, and a bar code system would require complete consistency of medication orders between pharmacy and nursing staffs. In addition, bar code technology may achieve efficiencies in other laboratories as well. If so, the total estimated annual efficiency gains to an average hospital would range from $272,900 to $436,600 from use of bar code scanners in pharmacies and patient care wards. If such gains were obtainable, the PV of these gains for the sector as a whole would be between $4.0 billion and $6.4 billion with a 7 percent annual discount rate. The PV of this potential gain would be between $5.3 billion and $8.5 billion if a 3 percent discount rate is used in the calculation. The average annualized gains of these potential efficiencies are between $376.3 million and $602.0 million (at 7 percent), or $359.0 million and $574.2 million (at 3 percent).

The final rule could also increase the use of medical informatics in locations other than hospitals. Health care facilities such as physician offices, nursing homes, long-term care facilities and home health delivery systems would be more likely to adopt bar coding and scanning systems to safeguard the use of patient medications and achieve additional efficiencies. However, ERG's analysis of the adoption of bar code technology in nursing homes and long-term care facilities does not indicate a rapid adoption at this time.

According to the AHCA, there are 16,456 nursing homes in the United States. ERG estimates the initial investment for an average nursing home to install a bar code system to be $221,400 and to have annual operating, maintenance, and net efficiency costs of $67,000. Most costs are for purchasing laptop computers for nursing wards as well as training costs. The major study of preventable ADEs in nursing homes (Ref. 17) has estimated that there are only 10,373 preventable ADEs per year in nursing homes attributable to dispensing or administration, or less than 0.67 preventable ADEs per facility. If the use of a bar code system could intercept 50 percent of these ADEs, the benefit per facility per year would equal 0.32 ADEs. There are strong indications that these estimates of prevented ADEs are conservative because the study is based on voluntary reporting.

Comparisons between the drug classes associated with ADEs in nursing homes (Refs 17 and 18) and those in hospitals resulted in a distribution of expected outcomes of ADEs different than those in hospitals. For example, Bates (Ref. 2) found that 38 percent of all preventable ADEs were associated with analgesics and antibiotics, while in nursing homes, only 13 percent of all ADEs were associated with these drug classes. Using the distribution of drug classes associated with preventable ADEs in nursing homes, the weighted average value of a prevented nursing home ADE was $43,200 (7 percent) and $63,700 (3 percent). These estimated values are based on very limited analyses conducted to date in nursing homes.

Forecasted adoption rates for nursing homes resulted in PV of costs of $3.8 billion and PV of benefits of only $0.5 billion (7 percent). At 3 percent the PV of costs to nursing homes was $4.9 billion while the PV of ADE avoidance was only $0.6 billion. With profit margins so slight in this industry, we do not believe the technology will be rapidly adopted at this time in spite of the accessibility of bar coded products. We emphasize the current scarcity of data on ADEs in nursing homes. The definition of ''preventability'' used to analyze ADEs in hospitals may not transfer to these settings, which may severely under estimate the potential benefit. However, we cannot project impacts of this rule for this industry at this time.

M. Distributional Effects of Bar Code Technology

Bar code usage would likely result in distributional transfers between sectors of society. For example, bar code use could reduce hospital payments due to punitive damage awards from potential lawsuits. According to legal data bases (Ref. 19), there were approximately 35,000 personal-injury and malpractice claims per year between 1995 and 2000 in the health care sector. Approximately half of these claims were for pregnancies with the remainder including surgical claims, misdiagnosis, and medication errors. If these claims are distributed equally by type (surgical, diagnosis, or medication errors) and sector (inpatient or outpatient), we estimate that about 600 legal claims per year are potentially associated with preventable ADEs in hospitals. This implies that only 0.2 percent of all preventable ADEs are likely subject to legal claims (600 divided by 373,000). The average jury award for damages from medication errors was $636,800 in 2000, although only 40 percent of cases were decided for plaintiffs. Estimated average pre-trial settlements for malpractice claims in 2000 totaled $318,400. We do not have data on the proportion of settlements, but have assumed 80 percent of claims are settled prior to trial. If so, the average likely award per preventable ADE is $492. Current bar code systems are expected to avoid 16.7 ADEs per year in an average hospital. This implies an average reduction in annual legal awards of $8,200 per hospital and $41.4 million for all hospitals. Fewer awards would result in lower malpractice insurance premiums, which would reduce other hospital expenditures. The General Accounting Office (Ref. 20) reported hospital malpractice insurance rates ranging between $511 and $7,734 per bed depending on location. Recent reports have suggested that annual premiums have increased to about $4,228 to $11,435 per bed (Ref. 21). Although only a weak relationship has been established between negligent acts and the incidence of malpractice claims (Refs. 22 to 24), we attempted to estimate the potential size of any impact on premiums. Rothchild et al (Ref. 25) estimated that only 6.3 percent of all malpractice claims were the result of ADEs. Given the distribution of ADEs in

the medication process, we expect a 50 percent reduction in ADEs caused by distribution and administration errors to reduce premiums by 0.55 percent, or $49 per bed to the average hospital. The total expected saving would be $8,330 per hospital and $42.0 million for all hospitals. While reductions in legal settlements or liability insurance premiums represent transfers between hospitals, third-party payers, attorneys, and patients and are not opportunity gains or losses, such reductions could increase the efficient allocation of resources by sector.

Bar code systems may also increase hospital revenues by improving the ''cost capture rate.'' One published study (Ref. 26) reported the cost capture rate (the ratio of billed uncontrolled pharmaceuticals to all pharmaceuticals used) increased from 63 percent to 97 percent after installation of computerized systems in nursing wards. According to the authors, this would imply an increase in revenues of about $65,000 per year for an average hospital. While such accounting improvements are transfers from patients and third-party payers to hospitals rather than reduced opportunity costs, this practice illustrates the potential use of bar code scanning systems in increasing the efficient allocation of resources by sector. Other potential transfers may include avoidance of certain billing errors or increased timeliness of payment.

N. Comparison of Costs, Expenditures, and Benefits

The increase of over 780,000 QALYs over the evaluation period as a result of avoiding over 500,000 ADEs and AHTRs has a monetized present value of $54.8 billion (discounting at 7 percent) and $73.0 billion (discounting at 3 percent). This section compares the expected benefits of the regulation to the costs and expected expenditures discussed earlier.

The annualized costs of the final rule to the manufacturing, packaging, and labeling sectors totals $5.4 million (7 percent) or $4.1 million (3 percent). Hospitals would be required to incur an annualized cost of $0.6 million to continue current operating practices (7 percent) or $0.4 million (3 percent). FDA's resource costs to support the regulation equal an estimated $2.4 million per year. Thus, we estimate the annualized regulatory cost of the regulation to be $8.4 million (7 percent) and $6.9 million (3 percent). In addition, we expect the rule to spur earlier investment by hospitals in bedside point-of-care systems that read bar coded labels. The annualized opportunity cost of this accelerated investment in technology is $660 million (7 percent) for the entire industry, or $600 million with a 3 percent discount rate. Table 7 presents, by sector, the present value of the estimated regulatory costs, the annual costs expected at the end of the 20-year evaluation period, and the annualized costs over the entire evaluation period for both discount rates. The estimated reduction in hospital operating expenses results from the assumption that hospitals could eliminate in-house labeling operations once products have uniform bar code information.

TABLE 7.—COSTS AND OTHER EXPECTED EXPENDITURES OF THE FINAL RULE

Industry Sector	Present Value of Costs	Annual Operating Costs at End of Period	Annualized Costs
(in millions of dollars; 20-year evaluation period; 7-percent discount rate)			
Prescription Drugs	$33.6	$0.4	$3.2
OTC Drugs	$23.3	$0.3	$2.2
Blood Products	N/A	N/A	N/A
Sub-Total Manufacturers	$56.9	$0.7	$5.4
Hospital Regulatory	$6.4	(-$0.2)**	$0.6
Sub-Total Private Sector Regulatory Costs	$62.3	$0.5	$6.0
FDA Oversight	$25.4	$2.4	$2.4
TOTAL REGULATORY COSTS	$87.7	$2.9	$8.4
EXPECTED EXPENDITURES FROM HEALTH CARE SECTOR	$6,961.6	(-$17.7)**	$657.2
(in millions of dollars; 20-year evaluation period; 3-percent discount rate)			
Prescription Drugs	$37.0	$0.4	$2.5
OTC Drugs	$23.8	$0.3	$1.6
Blood Products	N/A	N/A	N/A
Sub-Total Manufacturers	$60.8	$0.7	$4.1
Hospital Regulatory	$5.5	(-$0.2)**	$0.4
Sub-Total Private Sector Regulatory Costs	$66.3	$0.5	$4.5
FDA Oversight	$35.7	$2.4	$2.4
TOTAL REGULATORY COSTS	$102.0	$2.9	$6.9

TABLE 7.—COSTS AND OTHER EXPECTED EXPENDITURES OF THE FINAL RULE—Continued

Industry Sector	Present Value of Costs	Annual Operating Costs at End of Period	Annualized Costs
EXPECTED EXPENDITURES FROM HEALTH CARE SECTOR	$8,971.4	(-$17.7)**	$602.9

*Less that $0.05 million
**Hospital operating costs decrease due to fewer in-house packaging and bar coding operations

As discussed above, we estimate the annualized public health benefit to be $5.2 billion (7 percent) and $4.9 billion (3 percent). This estimate includes the societal value of the avoided ADEs and AHTRs as well as the reduced hospital stays expected due to the earlier use of bar code reading technology. We estimate other indirect potential benefits, such as efficient inventory control, patient tracking, electronic generation of daily reconciliation and medication reports, or other administrative gains, to contribute an annualized amount of between $376.3 and $602.0 million in efficiency gains to hospitals (7 percent) and between $359.0 and $574.2 million (3 percent). The likely distributional effects of revenue enhancement, other cost capture measures, or reduced legal costs are not included in this comparison.

If all costs and expenditures are combined, the annualized outlays total $665.6 million (7 percent) and $609.8 million (3 percent). The expected annualized public safety benefit of over $5.2 billion (7 percent) and $4.9 billion (3 percent) far outweighs these outlays. Thus, the annual net benefits for the entire evaluation period are between $4.5 billion (7 percent) and $4.3 billion (3 percent). The expected cost effectiveness varies between $9,000 and $15,300 for each QALY gained, depending on the discount rate used. Moreover, this calculation does not account for the potential efficiency gains as described above.

O. Uncertainty and Sensitivity

We recognize that the expected impacts of the regulation are based on a large number of uncertain assumptions. We attempted to account for this uncertainty by examining the key assumptions in the analysis. Table 8 summarizes the results of our analyses.

TABLE 8.—SUMMARY OF UNCERTAINTY AND SENSITIVITY ANALYSES

Variable	Base Case Assumption	Alternative Assumption	Effect on Annualized Net Benefits (7 percent)	Total Annualized Net Benefit (millions)
Voluntary Share of Labeling Costs	50 percent	None	-$2.1 million	$4,498.00
	50 percent	100 percent	+$2.1 million	$4,502.00
Impact of Regulation On Unit of Use Package	N/A	N/A	No Impact Expected	$4,500.00
Implementation Period	2 Years	1 Year	-$0.1 million	$4,500.00
	2 Years	3 Years	+$0.1 million	$4,500.00
Mortality Probability With ADE	2.8 percent	1.0 percent	-$2.6 billion	$1,900.00
	2.8 percent	0.1 percent	-$3.8 billion	$700.00
Value of QALY/VSL	$373,000/QALY $5 million/VSL	$100,000/QALY $2 million/VSL	-$3.2 billion	$1,300.00
Boundary Analysis	N/A	N/A	Breakeven point requires gain of 103 years of hospital use of bar code technology as compared to baseline	N/A
Hospital Rate of Adoption of Bar Code Systems	20 year baseline 10 year with regulation	30 year baseline 20 year with regulation	-$1.3 billion	$3,200.00
	20 year baseline 10 year with regulation	20 year baseline 15 year with regulation	-$2.9 billion	$1,600.00
Increase in Interception Rate Attributable to Bar Codes	50 percent	20 percent	-$3.1 billion	$1,400.00
	50 percent	80 percent	+$3.1 billion	$7,600.00
Loss of Nursing Productivity	3 percent	1 percent	+$420 million	$4,900.00

TABLE 8.—SUMMARY OF UNCERTAINTY AND SENSITIVITY ANALYSES—Continued

Variable	Base Case Assumption	Alternative Assumption	Effect on Annualized Net Benefits (7 percent)	Total Annualized Net Benefit (millions)
	3 percent	5 percent	-$520 million	$4,000.00
Small Hospital Adoption	N/A	N/A	Annual net benefits of adoption of bar code systems for hospitals with 50 or fewer beds estimated at $47,000 per hospital.	N/A

1. Voluntary Share of Labeling Costs

The costs attributable to the final rule are the incremental costs above what the industry would incur in the normal course of business. As briefly discussed earlier, many drug products change labels, on average, as often as once a year for marketing or design reasons. The ERG estimate, however, assumes that 50 percent of the required labeling costs would be attributable to the final rule, due to the production process changes that would be required to use bar coding equipment. In addition, we believe that market driven label changes are not completely comparable to regulatory required changes. We reviewed the sensitivity of this assumption by examining the impact that would occur if no required re-labeling costs were attributable to the regulation or all re-labeling costs were attributable to the final rule. ERG found that these scenarios altered the current estimate of $5.4 million in annualized costs for manufacturers, repackers, relabelers, and private label distributors (7 percent) to a range of from $3.3 million (if all costs are considered voluntary) to $7.5 million (if no additional labeling costs are considered voluntary). Using a 3 percent discount rate, the annual labeling costs to manufacturers could vary from between $2.6 million and $6.1 million.

2. Packaging Decisions

We are sensitive to industry packaging decisions and asked our contractor to specifically assess the impact of the regulation on the future of unit-dose packaging (e.g. blister packs) trends. The concern was whether bar code printing would reduce the use of unit-dose packaging, because it would add more to its cost than to other formats. In general, ERG found that although the overall demand for the product is inelastic, the demand for a particular package type is more elastic, in that it is affected by relative prices to a greater degree. Industry contacts, however, noted that this impact is moderated because consumers of some OTC drug product are accustomed to blister packs, and manufacturers could lose market share if they abandon this format. Also, many hospitals require drug purchases to be in unit-dose form.

ERG concluded that although a bar code requirement would increase the relative cost of the unit-dose version of a product, the cost increment would not be great enough to significantly impact the market. In fact, ERG found that the expected reduction in hospital over-packaging could increase market demand for unit-dose products despite the cost difference. Thus, we expect that the final rule will not have a significant impact on product packaging choices.

3. Implementation Period

We were interested in the effects of shortening or lengthening the implementation of the regulation. However, discussions with hospital administrators indicated that the adoption rate of bar codes would not be noticeably accelerated with shorter implementation period. They felt that it was unlikely that investments would be made earlier. Therefore, benefits would be unlikely to change whether the implementation period was longer or shorter. The regulatory costs of compliance would increase with shorter implementation periods. At a 7-percent annual discount rate, the average annualized regulatory cost would increase from $8.4 million with a 2-year implementation period to $8.5 million with a one-year implementation period and decrease to $8.3 million with a 3-year period.

If a 1-year implementation date persuaded one hospital to invest 1 year earlier, 16.7 ADEs could be avoided. The value of avoiding these events is $3.1 million. In comparison, if a hospital invested in a bar code reading system a year earlier than it otherwise would have, it would have increased costs of about $620,000 based on amortization of investment and one additional year of operating costs. The net benefit ($2.5 million), when amortized over 20 years, would result in average annualized benefits of over $0.2 million. This is greater than the average annualized cost of the shorter implementation period. However, as noted earlier, discussions with hospital administrators and budget planners have not indicated that a shorter implementation period would have an effect on these investment decisions.

4. Value of Mortality Associated with ADEs

ERG estimated that 2.8 percent of preventable ADEs and 2 percent of all AHTRs are fatal. This was derived by averaging results from several medical studies. These studies relied on relatively small samples and varying methodologies. Due to the uncertainty attached to this estimate and the major impact this assumption has on valuing public health benefits, we tested two additional mortality rates: 1 percent and 0.1 percent. These rates reduce the expected value of an avoided ADE from $185,800 to $93,700 and $48,400, respectively, by changing the probability distribution of the expected outcomes of ADEs. The impact on the expected annualized benefits of ADE avoidance falls from $5.2 billion to $2.6 billion and $1.4 billion respectively. These estimated benefits continue to exceed the costs.

5. Value per QALY

There is no precise measure of value for a quality-adjusted life-year. We have used average published estimates of society's implied value of a statistical life (VSL) of $5 million derived from wage premiums required to attract employment to higher risk occupations. The life expectancy of a 35 year-old blue-collar male employee (the basis for most of the wage premium data) was adjusted for expected future bed and non-bed disability. When the implied VSL is amortized over the 41.3 years of adjusted life-expectancy using a 7 percent discount rate, the resulting value ($373,000) implies societal willingness-to-pay for a QALY. Cost-effectiveness studies have claimed that lower values, as low as $100,000, may better represent QALYs. In addition, the VSL value is based on research conducted in the early 1990's and relies on relative risk and relative wages. Other estimates of VSL have ranged

from as low as $2 million to as high as $10 million.

We analyzed the societal benefit of the regulation using $100,000 as the QALY value and the low VSL estimate ($2 million) as the representative of societal willingness to pay (WTP) to avoid the probability of a fatality. The WTP to avoid an ADE decreased from $185,800 to $71,600 using these parameters. Overall, the annualized benefit of the proposed regulation fell from $5.2 billion to $2.0 billion.

6. Boundary Analysis

We analyzed the minimum number of hospital-years of bar code adoption necessary for estimated benefits to exceed costs. The regulatory costs of the regulation account for only 0.2 percent of the net societal benefits. This implies that the regulation would need to encourage early adoption of bar code technology by at least 0.2 percent in order for benefits to exceed costs. In baseline, we expect 51,410 hospital-years of installed bar codes. (The 101 current user of bar code systems will use it for all 20 years, the remaining 4,939 hospitals will have installed systems for an average of 10 years each.) The regulation would have to encourage 103 additional hospital-years (0.02 percent). This could occur by 103 hospitals investing 1 year earlier than they would in baseline.

7. Hospital Response Rates

The expected benefits rely on a faster rate of hospital acceptance of bar code technology than the rate expected in the absence of the regulation. The current estimate of public health benefits is based on all hospitals acquiring bar coding systems within 10 years as compared to 20 years without the rule. However, because we are not requiring hospitals to make this investment, we examined the impact of different diffusion rates. ERG examined 2 additional scenarios; one in which the technology is accepted within 20 years with a rule as compared to 30 years without a rule as well as one in which technology is accepted within 15 years as compared to 20 with the rule. Both cases decrease costs and benefits. The first case reduced expected annualized net benefits from $4.5 billion to $3.2 billion. Annualized hospital expenditures declined from $657 million to $493 million and benefits decreased from $5.2 billion to $3.7 billion. The second case reduced annualized net benefits to $1.6 billion. Annualized hospital expenditures declined from $657 million to $320 million and benefits decreased from $5.2 billion to $1.9 billion. The public health benefits of the rule would still exceed costs and expenditures with these slower diffusion rates.

8. Hospital Intercept Rates with Machine-Readable Technology

Avoidance of patient ADEs depends on the expected rate of error interception. For this analysis, ERG found that about 45 percent of the errors that lead to preventable ADEs originate in the dispensing and administration stages of the medication process and that the use of bar coded information and installed systems would intercept about 50 percent of these errors. Because of the direct relationship between expected interception rates and avoided ADEs, we tested the impact of the assumed rates. Although the literature has implied that interception rates as high as 85 percent are obtainable, ERG assumed a 50 percent rate to account for potential non-optimal use of technology. If the true increase in interception rates were between 80 percent and 20 percent, the total number of avoided ADEs would be between 805,700 and 198,500. The monetized annualized value of these avoided ADEs would vary from the current estimate of $5.2 billion to the lower and higher values of $2.1 billion (with a 20 percent improvement in interception rates) or $8.3 billion (with an 80 percent improvement in interception rates). From a societal perspective, therefore, the accelerated technology investment appears reasonable even with significantly lower interception rates.

9. Productivity Losses in Hospital Wards

The decision by hospitals to make significant investments in bar code reading technology is highly dependent on expected productivity changes in the delivery of bedside care by nurses. Our current analysis assumes a 3 percent productivity loss of ward nurses due to the use of this new technology (see section VII.G). We examined the sensitivity of this estimate and found that if long-term productivity loss approximated only 1 percent of the current workload, the average annualized cost of accelerated hospital investments would decrease from $657.2 million to $238.4 million. However, if the productivity loss of nursing resources were as great as 5 percent, the annualized expenditures by hospitals would increase to $1.2 billion. In order for the productivity losses to outweigh the expected benefits, however, there would have to be an almost 700 percent estimated productivity loss.

10. Investments by Hospital Size

The internal decision to acquire and use new bar code reading technology could be affected by the size of the purchasing hospital. Hospitals that have already installed this equipment are, for the most part, fairly large or part of a large network of hospitals. Because the benefits of error interception are dependent on the number of annual admissions, we were concerned about the likelihood of technology adoption by small hospitals.

According to the most recent census, there are 1,218 hospitals in the United States with capacities fewer than 50 beds. These hospitals account for only about 3 percent of the estimated annualized opportunity cost of investment from this rule, because the potential productivity losses are not as great as for larger hospitals. The annualized opportunity costs per facility with fewer than 50 beds is about $69,200. However, because of the fewer admissions to hospitals of this size, we estimate that the interception rate of the bar code technology is expected to result in an average of 2.2 avoided ADEs per year per facility. The estimated societal benefit of avoiding 2.2 ADEs is $408,800. If these small hospitals adopt technology at the same accelerated rate as all hospitals, the annualized benefit per hospital is $116,900, or more than the investment.

We are aware that the estimated direct annual hospital cost savings of avoiding ADEs alone ($2,257 per avoided ADE) may not cover the costs of the expected earlier investment pattern. For example, the average facility with fewer than 50 beds would experience direct annual cost savings of $4,965 (2.2 ADEs avoided x $2,257) and annualized costs of $69,200. As noted, the investment decision to install bar code reading technology is voluntary and would include consideration of patient safety and other cost-savings. We have estimated that potential reductions in resources needed to generate reports and keep track of records may likely vary between $27,400 and $43,700 per year for a small hospital. Other institutional gains, including transfers such as increased revenue capture rates and reduced malpractice awards, may also affect internal decisions. Many industry representatives have indicated their willingness to invest in this technology. Nonetheless, even if some hospitals choose to delay or not to invest, this rule would still produce substantial societal benefits.

P. Small Business Analysis and Discussion of Alternatives

We believe the final rule is unlikely have a significant impact on a substantial number of small entities. Despite this, in the proposed rule, we prepared an initial Regulatory Flexibility Analysis (IRFA) and invited comment from affected entities. In addition, the final rule is considered a significant economic impact under UMRA and alternatives are examined and briefly discussed here.

1. Affected Sectors and Nature of Impacts

We described the affected industry sectors earlier in this section. The final rule directly affects manufacturers of pharmaceutical and biological products (NAICS 325412 and NAICS 325414), packaging services (NAICS 561910), and indirectly affect hospitals (NAICS 622). The regulation does not affect blood and organ banks (NAICS 621991). We accessed data on these industries from the 1997 Economic Censuses and estimated revenues per establishment. Although other economic measures, such as profitability, may provide preferable alternatives to revenues as a basis for estimating the significance of regulatory impacts in some cases, any reasonable estimate of profits would not change the results of this analysis. These revenues were updated to 2000 values by using the Consumer or Producer Price Index as appropriate.

a. *Pharmaceutical manufacturers (NAICS 325412).* The Small Business Administration (SBA) has defined as small any entity in this industry with fewer than 750 employees. According to census data, 84 percent of the industry is considered small. The average annual revenue for these small entities is $26.6 million per entity. Small manufacturers of prescription and OTC drug products dispensed pursuant to an order and commonly used in hospitals would be required to generate and label products with bar coded information. We estimate the annualized compliance costs for small entities in this industry at $1,800 per entity. This is less than 0.1 percent of their annual revenues. We believe this does not constitute a significant impact on a substantial number of small entities in this industry.

b. *Biological product manufacturers (NAICS 325414).* The SBA has defined as small any entity in this industry with fewer than 500 employees. According to census data, 68 percent of the industry is considered small. The average annual revenue for these small entities is $4.7 million per entity. Small manufacturers of biological products would be required to label products with bar coded information. We estimate the annual compliance costs for small entities in this industry at $600 per entity. This is less that 0.1 percent of their annual revenues. We believe this does not constitute a significant impact on a substantial number of small entities in this industry.

c. *Packagers (NAICS 5619190).* The SBA has defined as small any entity in this industry that has less than $6 million in annual revenues. On this basis, almost 75 percent of the industry is considered small. The average annual revenue for small entities is $1.7 million per entity. Small packagers would be required to apply bar coded information to all affected products. This would require printing and process improvements to packaging operations. We estimated the annualized compliance costs for small entities in this industry at $240 per entity. This is less than 0.1 percent of their annual revenues. We believe this does not constitute a significant impact on a substantial number of small entities in this industry.

d. *Blood and organ banks (NAICS 621991).* The SBA has defined as small any entity in this industry that has less than $8.5 million in annual revenues. On this basis, 40 percent of the industry is considered small. The average annual revenue for small entities is $1.4 million per entity. Small blood banks and collection centers currently apply bar coded information to all blood products and would not be affected by this regulation.

e. *Hospitals (NAICS 622).* The SBA has defined as small any entity in this industry with less than $29.0 million in annual revenues. According to census data, 35 percent of the industry is considered small. The average annual revenue for small entities is $12.6 million per entity. There is no specific regulatory requirement for hospitals to respond to this regulation. We anticipate that the rule would make the investment in bar code technology more attractive to hospitals, but the final rule does not require hospitals to make such investments. Hospitals that have already installed bar code reading systems and internally affix self-generated information might find it necessary to prematurely upgrade or replace currently installed scanners in order to capture bar coded information on small vials or bottles. These hospitals would also achieve productivity gains by avoiding the resources now used to self-generate bar code readable information. The total annual net cost of the regulation is estimated at $3,300 per facility, which is equal to less than 0.1 percent of their annual revenues. We believe this does not constitute a significant impact on a substantial number of small entities in this industry.

2. Alternatives

We considered several alternatives to the regulation. Each is discussed below.

a. *Do nothing.* This alternative would not result in any change in current labeling or packaging practices. We believe that in the absence of agency action, hospitals would gradually purchase and utilize independent bar code reading systems, but that it would take 20 years before they were installed in all facilities. We rejected this alternative because of the expected positive net benefits of the rule. Also, we believe that standardizing bar codes would generate additional health and production efficiencies for a variety of different health care sectors.

b. *Requiring variable information.* We considered requiring additional information in bar codes, such as expiration dates and lot numbers. The incremental benefit of this data would include improved inventory control and ease of recalls. In addition, we are aware that some firms are voluntarily applying this information. However, we were unable to quantify the potential public health benefits of this additional information and the estimated additional annualized cost of this alternative was $59.1 million. We did not select this alternative because we could not demonstrate that the added benefits would exceed the added costs.

c. *Covering all OTC drug products.* We considered requiring all OTC drug products to include bar coded information. This alternative is rejected because the additional costs do not appear to be justified by the expected benefits. At this time, most non-institutional settings are unlikely to have access to bar code reading systems. Therefore, we could not identify any significant reductions in ADEs due to this alternative. Including all OTC drug products would create estimated additional annualized costs to the manufacturing sector of $0.7 million. The expected annualized regulatory costs of the regulation therefore would increase from the current estimate of $8.4 million to $9.1 million with no additional quantifiable benefit.

d. *Exemption for small entities.* We considered exempting small entities, but rejected the alternative due to the modest projected impact of this initiative on small businesses and the lack of label standardization that would result. We will consider exemptions on

a product basis, not on the size of the affected entity.

e. *FDA selecting a specific symbology*. We considered requiring bar coded information with a specific symbology. The rationale for considering this option was to minimize uncertainty to hospitals in selecting systems that would be able to confidently read the specific language. We decided, however, that identifying a specific symbology might adversely impact future innovations in other machine-readable technologies. The selected alternative would allow individual facilities and suppliers to devise systems that would maximize their own internal efficiencies, as long as the standardized information could be accessed. The lack of consistent universal standards has been a major impediment to the use of this technology. As long as symbologies could be read within a single standard, however, the identified market failure would be overcome. In addition, the expected costs of this alternative would be much greater than the selected alternative. Annualized costs to manufacturers would increase to $19.0 million and significant costs would occur to the retail sector due to the need for accelerated upgrade or replacement of currently installed scanners. Retail pharmacies would incur annualized costs of $27.6 million. Consequently, we rejected the alternative of identifying a specific symbology.

3. Outreach

We conducted a public meeting on July 26, 2002, to solicit comments from the affected sectors. Interested parties from the health care sector, manufacturing sector, retail sector, and equipment suppliers provided comment and insight to the agency. In addition, we met with various industry groups in order to ensure viewpoints were appropriately considered. These insights affected the regulatory considerations, and additional outreach is planned during the regulatory process.

We also received over 190 comments on the proposed rule.

4. What Comments Did We Receive on Our Economic Analysis?

Several comments focused on the proposed rule's ''Analysis of Impacts'' discussion. The analysis summarized the rule's costs and benefits.

(Comment 76) The preamble to the proposed rule estimated that 4,229 packaging lines are used in 1,447 establishments (68 FR at 12519). One comment disagreed with this estimate. The comment, submitted by a medical gas firm, claimed that the rule would affect more than 1,000 members of the gases and welding distributors association and that 600 members package or distribute medical gases. The comment said there are approximately 10 major manufacturers of medical gas products in the United States, and many either own or control approximately 200 locations that repackage or distribute medical gas.

(Response) We agree that the proposed rule did not take this industry into account. However, because the final rule exempts medical gases from the bar code requirement, we do not need to adjust our analysis.

(Comment 77) The preamble to the proposed rule estimated the present value of the total costs to manufacturers, repackers, relabelers, and private label distributors as $33.2 million and average annualized costs of $3.2 million (68 FR 12520 through 12521).

Several comments claimed this estimate was too low. One comment from a medical gas firm said implementing the rule would cost $5 million for one firm and that annual maintenance and material costs cannot be accurately determined. The comment said that the cost to the medical gas industry alone would be over $100 million.

Two comments from allergenic extract firms also claimed high costs. One comment said that the firm would need to add 800 new NDC numbers and create new labels for its products. The comment claimed that the new labels would have to be printed by another company and it projected those costs as being $37,000 for required equipment and artwork, $39,000 for 640 hours of computer programming time to test and validate the new label format, $17,000 for inventory control, purchasing, and regulatory personnel time for internal control of each label and package change (based on an estimate of more than 530 hours at $31 per hour), $18,000 for changes in their standard operating procedure, and ''unknown, but substantial'' costs for locating a new vendor to prepare the new labels. The comment said these costs would be three or four times the firm's current $4,000 label costs and estimated its total costs as approximately $120,000. Another firm estimated its total cost as $166,500, excluding ''unknown, but substantial hidden costs required due to the small nature of some of our final containers.''

Three comments from pharmaceutical companies and a trade association also claimed the industry cost estimate was low. The comments said that manufacturers would have to purchase new or upgraded equipment to print high quality bar codes. One comment said that manufacturers would have to upgrade existing packaging equipment or buy new equipment, and those purchases would result in substantial investments that would exceed FDA's initial cost estimates.

(Response) We agree that specific firms will experience higher compliance costs than the average costs presented in the proposal and discussed in Reference 1 in the docket. However, ERG interviewed many companies, vendors, and industry consultants to arrive at their estimates of the incremental compliance costs for the affected industry. We agree that costs to medical gas and allergenic extract manufacturers were not explicitly accounted for in the proposal and that these industries are exempted from the final rule. We believe the methodology described in Reference 1 results in reasonable incremental costs of the final rule to industry. Our interviews with industry consultants have noted that many pharmaceutical manufacturers either currently use bar codes in their labels or are in the process of voluntarily applying bar codes. The costs attributable to the final rule are only those costs incurred in addition to voluntary costs. We disagree that the cost estimates to manufacturers, repackers, relabelers, and private label distributors do not reflect typical costs to typical firms.

(Comment 78) The preamble to the proposed rule estimated the regulatory costs to hospitals as being $6.1 million, with an average annualized cost of $0.6 million (68 FR 12521). One comment disagreed with this estimate, claiming that the rule would be very expensive for small State mental hospitals because manufacturers will pass on their costs to customers, and because wireless equipment (for reading the bar codes) will be even more expensive. The comment added that increases in package size will mean that automated drug dispensing machines will have to be stocked more frequently or small hospitals will have to carry more floor stock that is not controlled by such machines, which will reduce patient safety.

(Response) We disagree that the final rule will be very expensive for small hospitals. The final rule does not require small hospitals to invest in bar code technology, and we recognize that any such decision will be affected by individual circumstances. ERG did not find definitive evidence that regulatory costs are automatically passed on to customers, and we have analyzed these costs at the manufacturer level. In addition, we found no indication that

package sizes would definitely change as a result of this regulation. RSS symbology could be used so that no changes would occur in package size. We examined the impact of bar code technology on small hospitals as a sensitivity analysis.

(Comment 79) The preamble to the proposed rule mentioned that the American Hospital Association had stated that bar codes would help streamline payment, billing, and administrative systems and lead to efficient management of assets and resources (68 FR 12520).

One comment said that most inpatient reimbursement involves a high proportion of Medicare and Medicaid patients under a prospective payment or per diem basis, so increased accuracy of charge does not necessarily result in increased revenue. The comment said that costs associated with implementing bar code scanning would not be offset by increased reimbursement.

(Response) The comment may have misinterpreted the preamble to the proposed rule. We did not claim that bar codes would increase hospital revenue due to increased accuracy in billing. While we did present results that indicated the possibility of increased cost capture rates in the preamble, those distributive effects did not indicate reimbursement. Instead, the preamble to the proposed rule focused on cost savings in avoiding adverse drug events (68 FR at 12527), and we recognized that the estimated direct annual hospital cost saving of avoiding unnecessary treatment might not cover the costs of earlier investments. We stated that a hospital's decision to acquire and use bar code technology could be affected by the hospital's size. We only noted that increased reimbursement might be an additional benefit of the technology.

(Comment 80) The preamble to the proposed rule stated that the rule would result in premature replacement of scanners currently used in hospital pharmacies and treatment wards (68 FR at 12521). We estimated that the present value of the incremental costs of accelerated scanner replacement or upgrade to be approximately $13.7 million, with an average annualized cost to hospitals of early replacement of $1.3 million.

One comment claimed that the ''half-life'' of scanners is less that the proposed rule's 3-year implementation window. The comment claimed ''at least half of all scanners currently in use will have been retired or replaced'' by the time we would require all drugs to have a bar code. The comment said the remaining scanners would have some useful life remaining and could be used for other purposes.

(Response) We agree with this comment. The estimate of expected costs of replacing scanners in hospitals uses the expected useful life of scanners and the costs of upgrading current scanners. ERG estimated that scanners are replaced within 5 years. After the implementation period, scanners that do not have the capability to read RSS symbology that have not been replaced must be either replaced or upgraded. This was explained in Reference 1.

(Comment 81) One comment from a pharmaceutical manufacturer said that the health care system would not benefit if hospitals are forced to pay more for bar-coded products before they have systems in place to use those bar codes. The comment argued that hospitals should be able to keep buying OTC drugs at the lowest cost (usually the largest package size and without a bar code). The comment said this would let hospitals keep their costs down while they invest in bar code technology.

(Response) The comment misinterpreted the proposed rule. Neither the proposed rule nor the final rule requires hospitals to purchase only bar-coded OTC drugs. Hospitals will continue to be free to make purchasing decisions based on criteria that are best for individual facilities.

(Comment 82) One comment said that there was little analysis of the implementation costs on those who would use the bar codes other than to estimate that the speed of adoption will double. The comment said we should evaluate the implementation costs.

(Response) We disagree with this comment. ERG and FDA have conducted detailed analyses to estimate implementation costs to users. These analyses are available in Reference 1, in the docket for the proposed rule, and summarized in the Analysis of Impacts.

(Comment 83) The preamble to the proposed rule considered various regulatory alternatives, including selection of a specific symbology (68 FR 12529).

One comment supported requiring the use of DataMatrix, claiming that DataMatrix has a minimal cost difference to implement when compared with linear bar coding symbologies, and that such costs will continue to decline. The comment claimed that 70 percent of packaging lines are already DataMatrix capable, and this would allow implementation at the lowest cost and in the shortest time.

(Response) Although the comment discussed DataMatrix in the context of our economic analysis, the comment's focus is the use of DataMatrix rather than a linear bar code. We discuss issues regarding linear bar codes and other technologies, including DataMatrix, at comment 38, and we refer to our response there to explain why the final rule continues to require a linear bar code.

Q. Conclusion

We have examined the regulation and find that the expected benefits outweigh the costs and that the regulation would improve public health. Reference 1 provides a detailed analysis that includes references and support for the assumptions and estimates of this section.

R. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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15. Churchill, W. W., site visit with W. W. Churchill, Director of Pharmacy Services, Brigham and Women's Hospital, Boston MA by J. Eyraud and C. Franz both of the Eastern Research Group, April 7, 2002.

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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 201, 606, and 610 are amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

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

■ 2. Section 201.25 is added to read as follows:

§ 201.25 Bar code label requirements.

(a) *Who is subject to these bar code requirements*? Manufacturers, repackers, relabelers, and private label distributors of a human prescription drug product or an over-the-counter (OTC) drug product that is regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act are subject to these bar code requirements unless they are exempt from the registration and drug listing requirements in section 510 of the Federal Food, Drug, and Cosmetic Act.

(b) *What drugs are subject to these bar code requirements*? The following drug products are subject to the bar code label requirements:

(1) Prescription drug products, however:

(i) The bar code requirement does not apply to the following entities:

(A) Prescription drug samples;

(B) Allergenic extracts;

(C) Intrauterine contraceptive devices regulated as drugs;

(D) Medical gases;

(E) Radiopharmaceuticals; and

(F) Low-density polyethylene form fill and seal containers that are not packaged with an overwrap.

(ii) The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

(2) Biological products; and

(3) OTC drug products that are dispensed pursuant to an order and are commonly used in hospitals. For purposes of this section, an OTC drug product is ''commonly used in hospitals'' if it is packaged for hospital use, labeled for hospital use (or uses similar terms), or marketed, promoted, or sold to hospitals.

(c) *What does the bar code look like*? *Where does the bar code go*?

(1) Each drug product described in paragraph (b) of this section must have a bar code that contains, at a minimum, the appropriate National Drug Code (NDC) number in a linear bar code that meets European Article Number/Uniform Code Council (EAN.UCC) or Health Industry Business Communications Council (HIBCC) standards. Additionally, the bar code must:

(i) Be surrounded by sufficient blank space so that the bar code can be scanned correctly; and

(ii) Remain intact under normal conditions of use.

(2) The bar code must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act.

(d) *Can a drug be exempted from the bar code requirement*?

(1) On our own initiative, or in response to a written request from a manufacturer, repacker, relabeler or private label distributor, we may exempt a drug product from the bar code label requirements set forth in this section. The exemption request must document why:

(i) compliance with the bar code requirement would adversely affect the safety, effectiveness, purity or potency of the drug or not be technologically feasible, and the concerns underlying the request could not reasonably be addressed by measures such as package redesign or use of overwraps; or

(ii) an alternative regulatory program or method of product use renders the bar code unnecessary for patient safety.

(2) Requests for an exemption should be sent to the Office of New Drugs (HFD-020), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (requests involving a drug product) or to the Office of Compliance and Biologics Quality (HFM-600), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852 (requests involving a biological product).

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

■ 3. The authority citation for part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 4. Section 606.121 is amended by revising paragraph (c)(13) to read as follows:

§ 606.121 Container label.

* * * * *

(c) * * *

(13) The container label must bear encoded information in a format that is machine-readable and approved for use by the Director, Center for Biologics Evaluation and Research.

(i) *Who is subject to this machine-readable requirement*? All blood establishments that manufacture, process, repack, or relabel blood or blood components intended for transfusion and regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(ii) *What blood products are subject to this machine-readable requirement*? All blood and blood components intended for transfusion are subject to the machine-readable information label requirement in this section.

(iii) *What information must be machine-readable*? Each label must have machine-readable information that contains, at a minimum:

(A) A unique facility identifier;

(B) Lot number relating to the donor;

(C) Product code; and

(D) ABO and Rh of the donor.

(iv) *How must the machine-readable information appear*? The machine-readable information must:

(A) Be unique to the blood or blood component;

(B) Be surrounded by sufficient blank space so that the machine-readable information can be scanned correctly; and

(C) Remain intact under normal conditions of use.

(v) *Where does the machine-readable information go*? The machine-readable information must appear on the label of any blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

* * * * *

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

■ 5. The authority citation for part 610 continues to read as follows:

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

■ 6. Section 610.67 is added to read as follows:

§ 610.67 Bar code label requirements.

Biological products must comply with the bar code requirements at § 201.25 of this chapter. However, the bar code requirements do not apply to devices regulated by the Center for Biologics Evaluation and Research or to blood and blood components intended for transfusion. For blood and blood components intended for transfusion, the requirements at § 606.121(c)(13) of this chapter apply instead.

Dated: January 6, 2004.

Mark B. McClellan,

Commissioner of Food and Drugs.

Dated: February 4, 2004.

Tommy G. Thompson,

Secretary of Health and Human Services.

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