DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 606, and 610

[Docket No. 02N–0204]

RIN 0910–AC26

Bar Code Label Requirement For Human Drug Products and Blood

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing a new rule that would require certain human drug product labels and biological product labels to have bar codes. The bar code for human drug products and biological products (other than blood and blood components) would contain the National Drug Code (NDC) number in a linear bar code. The proposed rule would 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 proposed rule would also require the use of machine-readable information on blood and blood component container labels to help reduce medication errors.

DATES: Submit written or electronic comments on this proposed rule by June 12, 2003. Submit written comments on the information collection requirements by April 14, 2003.

ADDRESSES: Fax written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Fax electronic comments to http://www.fda.gov/dockets/ecomments. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), Attn: Stuart Shapiro, Fax: (202) 395–6974.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy, Planning, and Legislation (HF–23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3380.

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I. Introduction

A. What Actions Led to This Rulemaking?

In 1999, the Institute of Medicine (IOM) issued a report entitled ''To Err Is Human: Building a Safer Health System'' (Ref. 1). (The IOM is a private, nonprofit organization that provides health policy advice under a congressional charter granted to the National Academy of Sciences.) The IOM report cited studies and articles to estimate that between 44,000 and 98,000 Americans may die each year due to a range of medical mistakes made by health care professionals. The IOM report estimated that, in 1993 alone, an estimated 7,000 deaths were attributable to medication errors (Ref. 1 at p. 27) and that:

• Medication errors account for 1 out of every 131 outpatient deaths, and 1 out of every 854 inpatient deaths (Ref. 1 at p. 27); and

• The death rate attributable to medication errors may be increasing. The IOM report cited a study that examined death certificates from 1983 to 1993. The study found that, in 1983, 2,876 deaths were due to medication errors (which the authors defined as accidental poisoning by drugs, medicaments, and biological products resulting from acknowledged errors by patients or health care professionals) (Ref. 1 at p. 32, Ref. A–14 of the Appendix to this document). In 1993, 7,391 deaths were attributed to medication errors, a 2.57-fold increase in the death rate (Ref. 1 at p. 32). Moreover, a comparison of outpatient death rates suggested nearly an 8-fold increase in medication error death rates (Ref. 1 at pp. 32 and 33).

The IOM report stated that deaths due to medication errors are often preventable and cited bar codes as one way to prevent them (Ref. 1 at pp. 37, 175, 188, 189, 195–196).

The IOM report generated considerable controversy. Some felt that the IOM's figures were exaggerated (Ref. 2), while others felt the figures might have been too low (Ref. 3). Some felt that the term ''medical errors'' was, itself, misleading (Ref. 4). Others, including FDA, suggested that the IOM report's basic message—that medical errors are a serious public health problem—should not be lost regardless of whether the annual mortality was 10,000 or 100,000 (Ref. 5)

The IOM report led to new efforts to improve patient safety. For example:

• In December 1999, President Clinton directed the HealthCare Quality Task Force to analyze the IOM report and to report back on recommendations to

protect patients and to promote safety. In February, 2000, he announced a plan to reduce preventable medical errors by 50 percent within 5 years.

• In February 2000, the Quality Interagency Coordination (QuIC) Task Force (a group composed of the Department of Health and Human Services (DHHS) and other Federal agencies) issued an action plan that highlighted steps for Federal agencies to take to reduce medical errors and to improve patient care.

• In March 2001, the Agency for HealthCare Research and Quality (AHRQ) issued a report entitled ''Reducing and Preventing Adverse Drug Events to Decrease Hospital Costs.'' The report stated that more than 770,000 people are injured or die each year in hospitals from adverse drug events and that studies had suggested that 28 to 95 percent of adverse drug events could be prevented by reducing medication errors through the use of computerized monitoring systems, especially computerized medication ordering systems (Ref. 6).

• In April 2001, the Secretary of Health and Human Services, Tommy G. Thompson (Secretary Thompson), announced the establishment of a new Patient Safety Task Force within DHHS. Secretary Thompson named FDA as one of the Federal agencies leading this new effort (Ref. 7).

Congress also focused its attention on patient safety by holding hearings in 2000 and 2001 on patient safety and medical errors. On May 24, 2001, Secretary Thompson appeared before the Senate Committee on Health, Education, Labor, and Pensions' Subcommittee on Patient Health and stated that new technology, such as bar coding, could help save lives and money. Secretary Thompson noted that other industries used bar coding and that the same technology could be used to track drug dispensing and use and to prevent medication errors (Ref. 8).

Shortly thereafter, the American Society for Health-System Pharmacists (ASHP) wrote to Secretary Thompson to urge that FDA ''develop regulations that mandate that drug manufacturers provide a standardized machine-readable code (bar coding) on all drug product containers, including single unit containers, which are essential for hospital unit dose drug distribution systems'' (Ref. 9). ASHP mentioned a June 26, 2001, recommendation by the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) urging FDA and the United States Pharmacopeia (USP) to establish and implement a uniform bar coding program for drugs (Ref. 9 at pp. 1 and 2). Secretary Thompson later asked FDA to begin working on a bar coding proposal, thereby putting in motion the events that led to this proposed rule.

B. What Are Medication Errors?

NCCMERP [1] defines a medication error as:

> * * * any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice; healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. (Ref. 10)

For purposes of this preamble, we will adopt the same definition of ''medication error.''

Medication errors are a part of the overall ''medical errors'' problem because medical errors include surgical errors, device failures, and medication errors. Medication errors can occur at several points from the time the physician selects the drug to prescribe 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.

Articles discussing medication errors can be found dating back several decades, and refer to such errors under various names, including ''preventable adverse events,'' ''drug misadventuring,'' and ''iatrogenic illness'' or ''iatrogenic injury.'' (The word ''iatrogenic'' refers to ''any adverse condition in a patient occurring as the result of treatment by a physician or surgeon'' (see *Dorland's Illustrated Medical Dictionary*, 26th ed., at p. 647).) The articles often identify the following types of medication errors:

• Administering the wrong dose,

• 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 or missing doses.

(See the Appendix elsewhere in this document for a description of various studies identifying different types of medication errors.)

C. How Frequently Do Medication Errors Occur? What Is Their Impact?

Studies differ as to how frequently medication errors occur. Some studies suggest that the medication error rate is under 7 percent, whereas others suggest a medication error rate at or above 20 percent. The differences may be due, in part, to different definitions of ''medication error'' or different research methodology that focused on fatalities, injuries, or medication orders. (See the appendix for a summary of medication error rates reported in several studies.)

Although most medication errors do not result in harm to patients, medication errors can result and have resulted in serious injury or death (Ref. 11).

Medication errors also represent a significant economic cost to the United States. In an article published in 1995, Johnson and Bootman estimated the direct cost of preventable drug-related mortality and morbidity to be $76.6 billion annually, with drug-related hospital admissions accounting for much of the cost (Ref. 12). The authors suggested that indirect costs, such as those relating to lost productivity, might be two to three times greater than the direct costs, making the total cost of all preventable, drug-related mortality and morbidity range from $138 to $182 billion. A study by Ernst and Grizzle published in 2001 used updated figures and revised the direct cost estimate to $177.4 billion (Ref. 13). Another article estimated the cost of preventable adverse drug events in hospitalized patients to be $5,857 for each adverse drug event and the estimated annual costs for preventable adverse drug events for a 700–bed hospital to be $2.8 million (Ref. 14).

D. How Would Bar Coding Help Prevent Medication Errors?

Bar codes would be part of a system, along with bar code scanners and computerized databases, that would enable 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. Under this model, the system could work as follows:

• A patient would have his or her drug regimen information entered into a computerized database.

[1] NCCMERP is composed of over 20 national organizations (including FDA) whose objectives are to increase the reporting, understanding, and prevention of medication errors and to recommend strategies relative to systems modifications, practice standards, and guidelines, and changes in packaging, labeling, and product identity.

• 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 use bar code scanners to read a bar coded wrist band 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 was 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 could also complement other efforts to reduce medication errors.

• In computer physician order entry (CPOE) systems, a physician enters orders into a computer instead of writing them on paper. The order can be checked against the patient's records for possible drug interactions, overdoses, and patient allergies (Ref. 26).

• The retail pharmacy community is beginning to use a bar-coded NDC number to verify that a consumer's prescription is being dispensed with the correct drug. These pharmacy-based systems compare a bar code that the pharmacy's computer prints on the consumer's prescription against the bar code on the drug's label. If the computer detects an error, the computer alerts the pharmacist to the problem.

In addition, bar codes could make it easier to enter medication order entries into a patient's electronic medical records, help in inventory control and billing, and help conserve hospital or health care staff resources or free those resources so that they can be devoted to patient care.

E. Can Bar Code Use Reduce the Incidence of Medication Errors?

Published articles and other information submitted to FDA suggest that bar coding can reduce medication error rates significantly.

• One New Hampshire hospital reduced its medication error rate by 80 percent after it adopted a bar coding program (Ref. 15).

• A medical center in Colorado lowered its medication error rate by 71 percent between 1992 and 1994 (Ref. 16).

• A Department of Veterans Affairs (VA) hospital in Kansas had no medication errors when its computerized, bar coding system was used properly; the hospital estimated that the system prevented over 378,000 medication errors in a 5-year period (Ref. 17).

• Other published articles have discussed how bar coding can reduce medication errors, including missed doses, or increase drug dispensing accuracy (Refs. 18 through 23).

At a public meeting that we (FDA) held on July 26, 2002 (67 FR 41360, June 18, 2002), the VA gave a presentation on its use of bar codes at the VA Medical Center in Topeka, Kansas. The VA stated that a comparison of medication error data from 1993, the last year before the VA implemented the bar code system, to data for 2001 showed that the Topeka medical center reduced its reported medication error rate by 86.2 percent (Ref. 24). The improvements included:

• 75.5 percent improvement in errors caused by the wrong medication being administered to a patient;

• 93.5 percent improvement in errors caused by the incorrect dose being administered to a patient;

• 87.4 percent improvement in wrong patient errors; and

• 70.3 percent improvement in errors caused when medications scheduled for administration were not given. (Ref. 24 at p. 14).

One comment submitted in response to the public meeting indicated that a bar code scanning system, in conjunction with a robotic system for pharmaceutical distribution, reduced dispensing errors at the University of Wisconsin from 1.43 percent to 0.13 percent and that the university realized a return on its investment in 2 years (Ref. 25). The comment also stated that there was an 89 percent reduction in medication administration errors due to point-of-care bar code scanning (Ref. 25 at p. 6).

We discuss the public meeting in greater detail in section II of this document.

F. Is There Support for Putting Bar Codes on Drug Products?

In recent years, many organizations have either commented favorably on or recommended the adoption of bar coding to reduce medication errors. These organizations include the QuIC Task Force, NCCMERP, ASHP, and Premier, Inc., an alliance of not-for-profit hospital and health care systems (Refs. 27 through 29).

We also saw considerable support for bar coding at the July 26, 2002, public meeting we held to discuss a possible rule to require bar code labeling. Nearly 400 individuals attended the meeting, and they represented a broad range of interests, including:

• Nurses, including the American Academy of Nursing;

• Pharmacists, including the American Society of Health-System Pharmacists;

• Physicians, including the American Medical Association;

• Hospitals, including the American Hospital Association, the VA, which already has a bar code program in place for drugs used in VA hospitals, and the Hospital Corporation of America, Inc., which intends to have bar coding technology in place in its hospitals by the end of 2005;

• Pharmaceutical manufacturers, including the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Generic Pharmaceutical Association (GPhA);

• Over-the-counter (OTC) drug manufacturers, including the Consumer HealthCare Products Association (CHPA);

• Medical device manufacturers, including the Advanced Medical Technology Association (also known as AdvaMed);

• Blood centers and blood organizations, including the American Association of Blood Banks, America's Blood Centers, and the American Red Cross;

• The Vaccine Identification Standards Initiative (VISI), a collaborative effort between public health agencies and private organizations involved in immunization practices and whose purpose is to establish voluntary, uniform guidelines for vaccine packaging and labeling and recording identifying information;

• Bar coding and other ''automatic identifier'' interests, including the Uniform Code Council and the Health Industry Business Communications Council (two standards development organizations that have established bar code standards);

• Health or medical product distributors, including McKesson

Corporation, the HealthCare Distribution Management Association, and Cardinal Health; and

• The USP.

In addition, in response to requests to discuss bar code issues in greater detail, we met separately with PhRMA on August 19, 2002, with CHPA, GPhA, and others on September 17, 2002, and with the National Alliance for Health Information Technology on October 9, 2002.

In general, almost all individuals, companies, and organizations attending or commenting on the public meeting strongly supported the use of bar codes on human drug products to help reduce medication errors, but differed in their opinions as to the information that should go into the bar code and whether certain products, such as over-the-counter (OTC) drugs and medical devices, should have a bar code. We discuss various aspects of the public meeting throughout the remainder of this preamble to show how information from the public meeting helped shape this proposal.

II. Description of the Proposed Rule

The proposal would create a new § 201.25 entitled ''Bar Code Label Requirements.'' The proposal would address:

• Who is subject to these bar code requirements?

• What drugs are subject to these bar code requirements?

• What does the bar code look like?

• Where does the bar code go?

The proposed bar code requirement would also apply to biological products (other than blood and blood components). We cross-reference this requirement in the biologics regulations at new § 610.67.

For blood and blood components, the proposal would amend part 606 (21 CFR part 606) in § 606.121(c)(13) which currently allows, but does not require, the use of machine-readable symbols, approved by the Director of the Center for Biologics Evaluation and Research (CBER), on blood and blood component container labels. The proposal would require the use of encoded, machine-readable information approved by the CBER Director on blood and blood component labels.

A. Who Would Be Subject to the Bar Code Requirement? (Proposed § 201.25(a))

In brief, under proposed § 201.25(a), manufacturers, repackers, relabelers, and private label distributors of human prescription drug products and OTC drug products regulated under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service 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(g)(1)). In practice, this means that pharmacies which are exempt under section 510(g) of the act are not required to put bar codes on drugs they are dispensing. (The requirements in proposed § 201.25 would apply to biological products (other than blood and blood components) and would include a cross-reference at proposed § 610.67. For convenience, this preamble will refer only to proposed § 201.25 alone without repeated cross-references to proposed § 610.67 (see section II.I of this document).) For purposes of this proposal:

• ''Manufacturer'' means a person or persons who owns or operates an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a drug by chemical, physical, biological, or other manipulations of the drug. These activities include repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the drug's distribution from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user.

• ''Repacker'' means a person or persons who owns or operates an establishment that repackages and relabels a drug and does not engage in any other activities performed by a manufacturer.

• ''Relabeler'' means a person or persons who owns or operates an establishment that affixes or changes labels on a drug and does not engage in any other activities performed by a manufacturer.

• ''Private label distributor'' means a person or persons who owns or operates an establishment that commercially distributes, under its own label or trade name, any drug manufactured, prepared, propagated, compounded, or processed by a manufacturer, repacker, or relabeler.

For example, if you make a prescription drug product, you would be subject to the bar coding requirement. However, if you are a pharmacy operating in conformance with applicable local laws regulating the practice of pharmacy and are regularly engaged in dispensing prescription drugs upon prescriptions of practitioners licensed to administer such drugs to patients, and do not manufacture, prepare, propagate, compound, or process drugs for sale other than in the regular course of business of dispensing such drugs at retail, you would not be subject to the bar code requirements. Your pharmacy would be exempt because section 510(g)(1) of the act does not require you to comply with the establishment registration and listing requirements.

We recognize that some hospitals themselves place bar codes on drugs and have reduced their medication error rates significantly. Requiring persons who manufacture, repackage, or relabel human drug products to bar code their own products should be more efficient and result in better quality bar codes. Manufacturers, repackers, and relabelers generally have sophisticated manufacturing processes and labeling machinery, and quality control systems that hospitals cannot afford. Bar coding by third parties (such as hospitals) would be more costly for the facility and would not achieve the economies of scale that larger entities could realize. Having many small entities affix bar codes could increase the possibility of a label error through the attachment of the wrong bar code and could lead to inconsistent bar code quality. For example, one comment from the public meeting stated that an institution administering 2.5 million doses per year, even if operating at 99.9 percent effectiveness at applying its own bar codes, would introduce seven new errors per day from repackaging. Another comment, submitted by an entity familiar with ''automatic identification'' methods, stated that ''on demand'' bar code printing, as used in hospitals and clinics, will have a higher error rate compared to bar code printing by manufacturers and that the ''use and maintenance of this type of bar code printing is historically haphazard at best.'' Another comment from a bar code standards organization estimated the error rate in hospital labeling to be approximately 17 percent nationwide.

More importantly, requiring persons who manufacture, repackage, or relabel human drug products and private label distributors to bar code their own products and to use the same bar coding standard should result in a more uniform bar coding system that can be used regardless of a patient's or hospital's location in the United States (Ref. 15). Uniformity should 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. Uniformity should also make it easier for manufacturers, repackers, relabelers, and private label distributors to put bar codes on products, because they would not have to customize their symbols or

bar codes to meet individual needs. (We discuss issues relating to the choice of a bar code symbology, standard, or other machine-readable format, and the potential impact on innovation, in detail in section II.D of this document.)

B. What Products Would Have to Have a Bar Code? (Proposed § 201.25(b))

1. What Did We Hear at the Public Meeting?

In the June 18, 2002, **Federal Register** notice (67 FR 41360 at 41361) announcing the public meeting on bar coding, we asked which medical products should have a bar code. We specifically invited comment on whether all prescription and OTC drugs should be bar coded, and we asked about blood products, vaccines, and medical devices (id.). We wanted our request for comments to help us decide which products should be covered by the proposal. For example, we sought information about OTC drugs because we did not know the costs and benefits of requiring all OTC drugs to have a bar code. For blood, we knew that an international bar coding standard (ISBT 128) existed, but did not know whether a rule requiring blood to have a bar code was necessary given that international standard. For vaccines, we were concerned that bar coding costs could have an adverse impact on vaccine manufacturers and vaccine supplies. For devices, our request for information was prompted by several letters to Secretary of DHHS Thompson, asking him to include devices in any bar coding rule (Refs. 31, 32, and 33).

The public comments we received reflected a variety of different positions. For example, almost all comments agreed that prescription drugs should have a bar code and that the bar code should extend to products at the unit dose level. However, comments from the pharmaceutical industry indicated that some products, such as samples, should not fall within a bar code regulation or that we should allow for exemptions. The USP also supported an exemption for certain containers, such as ampules or vials under 5 milliliters (mL).

For OTC drugs, many health care professionals supported bar codes on all OTC drugs, but other comments, including a comment from a trade association representing the OTC drug industry, disagreed, stating most OTC drugs are used in consumer settings where bar codes would not add value. The trade association also stated that all OTC drug products intended for retail sale have the universal product code (UPC) on the outer container and that there could be ''significant potential negative impact'' if we modified the UPC bar code system on OTC drug products. In contrast, one manufacturer of OTC drugs supported requiring bar codes on the outer container, but did not favor requiring bar codes for certain categories of products that carry little or no risk of causing adverse drug events in an institutional setting. CHPA and other companies repeated their concerns about bar codes for OTC drug products during a meeting with FDA on September 17, 2002, and emphasized the potential adverse impact on retailers if we required the UPC code to contain the NDC number. Some comments supported bar codes on OTC drugs used in hospitals or in ''institutional settings'' or OTC drugs packaged and sold for use in institutions.

A split between health care professionals and industry also existed for vaccines. For example, the Centers for Disease Control and Prevention, which coordinates the VISI program, recommended that vaccines have bar codes so that information on vaccines could be readily captured into medical records and other forms, thereby enhancing the monitoring of immunization programs and surveillance of adverse effects. Vaccine manufacturers, including VISI members, expressed a different view, stating that even small bar codes may be difficult to place on vaccines. One industry comment added that requiring bar codes on vaccines would ''increase the potential for disrupting vaccine production lines, particularly if there is a need for in-line printing'' and that ''[g]iven the fragile nature of vaccine supply and recent shortages of a number of vaccines, there is concern that any additional disruptions could exacerbate this situation.''

For blood, the comments generally agreed that we should require bar codes. Most comments acknowledged that an internationally standardized bar code symbology (ISBT 128) for blood exists and that the bar codes describe the blood's identification number, blood group and Rh type, product number, expiration date and time, and special testing results. However, while some comments recommended that we require blood containers to have bar codes using the ISBT 128 symbology, one comment, representing thousands of blood collection centers, blood banks, and transfusion services, opposed requiring the use of ISBT 128 through a regulation. Instead, the comment wanted us to require adoption of a United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components or ''focus on requiring electronic data interchange and the definition and use of standard data structures.''

For devices, the comments suggested another split between health care professionals and the regulated industry. Many health care professionals and hospital groups supported requiring bar codes on devices, although some would defer action on medical devices so that progress on a rule to require bar codes on drugs would not be slowed down. Others would defer action on medical devices because different device classes present different levels of risk. Device manufacturers generally opposed the inclusion of medical devices in a bar coding proposal. The device industry noted, as we did in our June 18, 2002, **Federal Register** notice (67 FR 41360) announcing the public meeting, that medical devices present different issues compared to drugs, biological products, and blood. For example, there are different classes of medical devices, and each class represents a different degree of risk, so, for a low-risk device (such as a bandage), a bar code might not have an impact on patient safety (67 FR 41360 at 41361). As another example, some medical devices may be reconditioned by parties other than the original manufacturer; in such situations, the original manufacturer might want to ensure that its bar code is removed or eliminated if the device is reconditioned, because the device no longer comes directly from the original manufacturer. Comments from device industry interests recommended further study and a separate rulemaking for devices or the voluntary use of ''automatic identifiers.'' However, one device manufacturer indicated that it already uses bar codes on its devices, but it uses the bar code for reimbursement purposes and for logistical reasons rather than for safety concerns. The manufacturer also recommended that, if we wanted bar codes on devices, we should issue guidelines instead of a rule.

2. What Products Would the Rule Cover?

After careful consideration of the comments, we propose to require the following products to carry a bar code:

- All prescription drug products, including biological products (including vaccines), but excluding physician samples; and
- Over-the-counter (OTC) drugs that are dispensed pursuant to an order and are commonly used in hospitals; and

For blood and blood components, the proposal would require the use of machine-readable information.

a. *Why Cover Prescription Drug Products, Including Vaccines, But Not Physician Samples*? The comments from the public meeting agreed that prescription drug products should have a bar code, although a small number of comments suggested that only prescription drug products used in institutions should be subject to a bar code requirement and that prescription drug samples should not be included.

We decided to cover all prescription drug products, rather than limit the rule to prescription drug products used in institutions, because we are unaware of any prescription drug products that are not used in hospitals. Our primary focus is to help reduce the number of medication errors occurring in hospitals, and, as we consider ''prescription drugs used in institutions'' as being the same as ''prescription drugs'' generally, the proposal refers to ''prescription drugs.''

However, with regard to prescription drug samples, we decided to omit prescription drug samples from a proposed bar code requirement because most samples are given to patients at physicians' offices, and we do 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 recognize that an argument could be made for including samples. We know that some samples are donated to charitable organizations, such as free clinics, for distribution to patients without charge (Ref. 34). These samples could be subject to the same medication errors as marketed prescription drugs, and those medication errors could be prevented through the use of bar codes. In addition, Congress and FDA have been concerned about illegal sales of prescription drug samples, the potential diversion of samples to illegal drug trafficking, and the entry of counterfeit drugs into the wholesale distribution system. Requiring bar codes on samples could help identify diverted or counterfeit drug products that enter distribution through illegal channels, and this could result in benefits that are not directly related to the prevention of medication errors.

We recognize that the vast majority of prescription drug samples are usually given to patients at physicians' offices and are not administered in hospitals. Because we have no evidence to suggest that physicians' offices are likely to be equipped with bar code scanners in the immediate future, the benefits associated with preventing medication errors through bar codes on prescription drug samples are unlikely to be realized in this health care setting. We also recognize that it is unlikely that charitable institutions, such as free clinics, would have the resources to buy bar code scanners to prevent medication errors. As a result, we have decided to omit prescription drug samples from the rule at this time. We do, however, invite comment on whether to require bar codes on prescription drug samples. Comments should address the costs and benefits associated with requiring bar codes on prescription drug samples.

The proposal would apply to vaccines. The National Childhood Vaccine Injury Act of 1986 (Public Law 99–660) (42 U.S.C. 300aa–25(a)) requires each health care provider who administers a vaccine set forth in the Vaccine Injury Table to any person to record, in that person's permanent medical record or in a permanent office log or file, the date of administration of the vaccine, the vaccine manufacturer, the vaccine's lot number, and other information. A bar code on vaccines could help ensure the accuracy of those records insofar as identification of the vaccine, its manufacturer, and date of administration are concerned, and, for those vaccines administered in health care facilities, help ensure that the right vaccine is administered to the right patient at the right time. However, we are sensitive to the vaccine manufacturers' concerns, particularly as they relate to possible adverse impacts on vaccine production or availability, and we invite comment on the risks and benefits of including vaccines in a bar code rule.

As for those comments that suggested an exemption for certain products or small containers, we decline to create an exemption mechanism and explain our reasons in section II.F of this document.

b. *Why Cover OTC Drugs That Are Dispensed Under an Order and Commonly Used in Hospitals*? The public meeting notice asked whether we should require bar codes on all OTC drugs. After reviewing the comments, we decided against requiring all OTC drugs to carry a bar code because it is unlikely that putting bar codes on all OTC drugs would have a significant impact on reducing medication errors and offset the large costs associated with requiring bar codes on all OTC drugs. Most OTC drugs are used outside hospitals and other health care facilities and are used by consumers who purchase the OTC drugs at retail. At this point, it is unlikely that individual consumers would buy, use, or have access to bar code scanners or use such scanners before taking an OTC drug.

We recognize, however, that some OTC drugs are administered to patients in hospitals and that bar codes would enable health care professionals to check whether they are giving the right OTC drug in the right dose and right route of administration to the right patient at the right time. In addition, we recognize that OTC drugs could interact with prescription drugs administered at that hospital or affect another drug's performance. Thus, we propose to require bar codes on OTC drugs that are dispensed pursuant to an order and are commonly used in health care facilities. For example, the bar code on an OTC drug dispensed pursuant to an order and commonly used in a hospital may allow a hospital's database to identify any potential interactions between the OTC drug and any prescription drugs prescribed for the patient, or may alert a health care professional to the patient's allergies relative to the OTC drug's ingredients. The proposal would apply to any manufacturer, repacker, relabeler, or private label distributor who sells a specific package of an OTC drug product to hospitals. It would not apply to all packages of a specific OTC drug product. An example of a specific package of an OTC drug product sold to hospitals would be an individual product, such as an aspirin tablet, packaged in a unit-of-use container.

We would interpret ''commonly used in hospitals'' to include OTC drugs that are sold to hospitals, packaged for institutional use, labeled for institutional use, or marketed, promoted, or sold to hospitals through drug purchasing contracts or catalogues. For example, if an OTC drug product manufacturer sends its catalogues to hospitals to solicit orders from them, the OTC drug products described in the catalogue would be ''commonly used in hospitals'' because the manufacturer is marketing its OTC drugs to hospitals. If a distributor relabeled an OTC drug ''for institutional use,'' then that OTC drug would be ''commonly used in hospitals'' because it is intended for hospital use.

We expect that manufacturers, repackers, relabelers, and private label distributors would know which of their products meet the definition of OTC drug products commonly used in hospitals. For example, we believe that when manufacturers, repackers, relabelers, and private label distributors label or package their OTC drugs for institutional use, they know that the products will likely be sold to hospitals. Manufacturers also know that their OTC drug products will be sold to hospitals when they market or promote those OTC drugs to hospital staff through detailing the products or other means, enter into hospital purchasing contracts, or sell to hospitals through catalogues.

We recognize that it is possible for a manufacturer to sell an OTC drug to a wholesaler or retailer who then re-sells the product, without making any changes to the product, directly to a hospital without the manufacturer's knowledge. We believe that, in most cases, the manufacturer would know that the product may be sold to a hospital (e.g., because of the product's labeling, packaging). However, there may be rare instances when the manufacturer may not have had reason to believe that its product would be sold to a hospital. Therefore, if the OTC drug is not packaged, labeled, marketed, promoted, or sold to a hospital as described above, we would not expect the OTC drug's manufacturer to comply with the bar code requirement.

Proposed § 201.25(b) would also include the phrase ''dispensed pursuant to an order'' with regard to OTC drugs. Some products in hospitals that are traditional types of OTC drugs, such as aspirin or acetominophen, are dispensed pursuant to a physician's order. Other products that are regulated as OTC drugs are not dispensed pursuant to a physician's order. For example, a hospital might provide fluoride toothpaste or mouth rinses to a patient without a physician's order. Because these products are not likely to contribute to medication errors, the proposal would focus only on those OTC drugs used in hospitals that are dispensed pursuant to an order.

We recognize that there may be other ways to describe the types of OTC drugs that should have a bar code. For example, we considered requiring bar codes for OTC drugs ''sold directly to hospitals.'' If the proposal pertained to OTC drugs sold directly to hospitals, most manufacturers, repackers, relabelers, and private label distributors who sold their products directly to hospitals would be subject to the rule, but the bar code requirement could be avoided by selling the OTC drugs to distributors or other third parties for re-sale to hospitals. We considered applying the bar code requirement to OTC drugs that are labeled for use in an institutional setting. This alternative is equally difficult to administer because it is easily circumvented by relabeling the drug. We considered requiring bar codes on OTC drugs commonly used in health care facilities (rather than hospitals), but could not determine whether clinics, nursing homes, and other facilities would invest in bar code scanning equipment.

We specifically invite comment on the terms we should use to describe OTC drugs that should be subject to the bar code requirement. Comments should also consider the following issues:

• Who should be required to apply the bar code on the OTC drugs that are subject to a bar code requirement? If the proposal refers to OTC drugs ''commonly used in hospitals,'' will manufacturers, repackers, and relabelers know which products require a bar code?

• Do the terms ''dispensed pursuant to an order'' sufficiently distinguish between those OTC drugs that are likely to be involved in medication errors from those that are not?

c. *Which Blood Products Are Covered*? Current FDA regulations state that the container label on blood and blood products ''may bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research'' (see 21 CFR 606.121(c)(13)), but they do not require the use of such symbols nor do they specify a particular symbol. Correct identification of blood is essential because transfusion errors or use of contaminated blood can have serious adverse health consequences for a patient. For example, one comment submitted in response to the public meeting stated that transfusion errors cause as many as two dozen patient deaths annually and that the number may be under reported. Consequently, we propose to require that blood and blood component container labels bear ''encoded information that is machine-readable'' and approved for use by the Director of CBER. We address this specific requirement at proposed § 606.121(c)(13), which we discuss more fully in section II.H of this document.

d. *Why Did We Omit Medical Devices From the Rule*? At this time, we are omitting medical devices from this rulemaking. We recognize that different issues arise for devices than for drugs, so further consideration is needed regarding the need for putting bar codes on medical devices. We will continue to study whether to develop a proposed rule to require bar codes on medical devices to prevent or reduce medication errors.

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

1. What Is the National Drug Code Number, and Why Would It Be Helpful?

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. Most persons attending the public meeting agreed that a bar code should, at a minimum, contain the drug's NDC number.

To complement this proposed requirement, we intend to revise our drug establishment registration and listing regulations to redefine the NDC number and to make the NDC number unique and more useful to informational databases, whether those databases are created for purposes of preventing medication errors, obtaining the latest information about a specific drug, or tracking drug use or distribution. We hope to publish a proposed drug establishment registration and listing rule in the **Federal Register** soon.

Please note that proposed § 201.25(c)(1) would require the bar code to contain, at a minimum, the NDC number. Several comments submitted in response to the public meeting indicated that some drug manufacturers already place bar codes on their products, but that the bar code contains a numerical identifier that contains, but is not identical to, the NDC number. For example, some comments suggested that the bar code contain the International Article Number (EAN) or the Global Trade Item Number (GTIN). We are aware that some drug companies already use a bar code containing the:

• Universal Product Code number (UPC). The UPC is usually a 12-digit number that may or may not contain the NDC number within it. For example, if the drug's NDC number were 1234567890, the UPC number might be 312345678906, where the first digit (3) signifies that the product is a drug, and the last digit is a ''check digit'' that helps confirm that the bar code was read correctly. However, some drugs, particularly OTC drugs, may have a UPC number that does not contain the NDC number;

• International Article Number (EAN). The EAN is a 13-digit number and also contains the NDC number within it; or

• Global Trade Item Number (GTIN). The GTIN is a 14-digit number that contains the NDC number in conjunction with a code that identifies the product's packing level. In the GTIN, the first digit signifies the packaging level.

Thus, under the proposal, the bar code could contain the NDC number alone or the UPC number, EAN number, or GTIN number, as long as the NDC number is present. By making the NDC number the minimum bar code information requirement, firms could continue using various numbering systems (such as the UPC, if the UPC number contains the NDC number, EAN, or GTIN numbers) in their bar codes, thus minimizing or eliminating the need for companies to redesign or generate new bar codes and

minimizing any disruptions to the companies' international markets.

We recognize that some comments supported the use of a unique identifying number rather than the NDC number. One comment explained that the UPC code that goes on the product label does not always use the NDC number, so if we required the bar code to contain the NDC number, important label changes could go unnoticed if health care professionals relied on the bar codes instead of product labels. The comment suggested that if distributors establish the unique identifying codes and revise those codes when they make label changes, the revised code could then trigger a need for a health care professional administering the drug to read the label and to update its database accordingly. Another comment described the NDC number as a ''dumb number'' in OTC drugs and suggested following UCC/EAN guidelines instead to identify the product. Another comment stated that OTC drugs should use the UPC number instead of the NDC number because changing UPC bar codes to include the NDC number would result in great expense without a discernable benefit. Additionally, during a meeting with CHPA and others, the industry representatives stated that UPC codes do not always contain NDC numbers, and retailers rely on the UPC codes, so requiring the use of NDC numbers would be disruptive to the industry and retailers. The industry representatives suggested using a unique identifier other than the NDC number.

We decline to require the use of unique identifying numbers other than the NDC number. Through the proposed drug establishment registration and listing rule, the NDC number would become a unique identifying number for listed drugs and correspond to a particular listed drug. If we allowed distributors to assign unique identifying numbers and did not coordinate the assignment of such numbers to drugs, the result could be extremely confusing as distributors could use different identification schemes (such as a mixture of letters, numbers, or other characters). Moreover, creating and maintaining databases on drug products for medication error purposes would become more difficult because identifying information would have to come from multiple sources. For example, the Federal Government might be the source for NDC number information, but firms who created unique, non-NDC identifying numbers would have to provide information on those numbers to the databases themselves if the databases are to be complete and useful. Multiple information sources 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. While we understand the OTC drug industry's reservations about changing UPC codes to include NDC numbers because of a possible impact on retailers, proposed § 201.25(b) would only require bar codes on OTC drugs that are dispensed pursuant to an order and are commonly used in hospitals, so most OTC drugs should not be affected.

2. Would the Bar Code Be Required to Contain the Lot Number and Expiration Date?

Many organizations and individuals have recommended that the bar code contain information regarding the drug's lot number and expiration date, and others have recommended phasing-in a requirement to have the bar code contain the lot number and expiration date.

We decline to require lot number and expiration date information in the bar code at this time. In general, while lot number and expiration date information would make it easier to identify drugs that had been recalled or were expired, we neither found nor received data to show that the benefits of bar coding lot number and expiration date information would exceed the costs of putting that information in the bar code. There is, however, limited information on the extent to which patient safety is affected by and medication errors occur as a result of taking expired or recalled drugs. We reviewed data from our adverse event reporting system (containing 71,546 cases) and found 90 cases where patients received an expired drug and 21 cases where patients received a recalled drug. Expired drugs may become subpotent and might not have the intended therapeutic effect. They also may contain degradation products associated with aging. Products may be recalled for a variety of reasons including no active ingredient present in the product or contamination of the product that could lead to infection.

We also tabulated data from the Office of Compliance, Center for Drug Evaluation and Research, on the reasons for and the extent to which drug products have been recalled from the market. From fiscal year 1997 through fiscal year 2002, there were 1,230 recalls, of which 97 were Class I (reasonable probability that the use or exposure to the violative product will cause serious adverse health consequences or death) and 1,133 were Class II (use or exposure of the violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote). Despite this number of recalls for safety and health reasons, we received few reports of adverse events associated with the administration of a recalled drug, and we do not have reliable data that show how often these products were administered to patients.

Thus, based on the data available to us, we cannot determine the magnitude of the public health problem associated with administering expired or recalled products, and we cannot quantify the patient safety benefit associated with requiring lot number and expiration date information in a bar code.

Some comments suggested that requiring lot number and expiration date information in a bar code could have benefits outside the medication error context by making it easier to track or trace products and to identify counterfeit products.

We agree that bar codes may be useful outside the medication error context, but our rule focuses on the use of bar codes to prevent medication errors.

Industry comments indicated that adding lot number and expiration date information to the bar code would adversely affect production line speed. One comment from a drug company predicted that encoding lot number and expiration date information would reduce packaging line speed by 40 percent and cost more than $4.8 million for its product lines. Another drug industry comment indicated that a requirement to encode lot number and expiration date information could cause companies to reconsider their packaging choices, or require companies to alter their printing methods.

We also note that inclusion of lot number and expiration date information might require the use of a different machine-readable format, such as a two-dimensional symbology, in addition to or as a substitute for a linear bar code, and that could affect a hospital's equipment purchasing decision. Use of nonlinear bar code formats could require the purchase of a different scanning or reading device and also increase a hospital's equipment costs.

Based on the evidence we had and our obligation under Executive Order 12866 to choose regulatory approaches that maximize net benefits, the potential burden of encoding lot number and expiration date information appeared to outweigh the potential benefit at this time. Consequently, the proposed rule

would not require lot number and expiration date information in the bar code. We will continue to study the issue and invite comments and, more importantly, data on costs and benefits associated with requiring lot number and expiration date information in the bar code. If comments provide information and data to support requiring lot number and expiration date information, we may consider requiring that information with the bar coded NDC number as part of a final rule.

Although the proposed rule would not require the drug's lot number and expiration date to appear in the bar code, the proposed rule would not prohibit the inclusion of such information. In other words, FDA will not object if a manufacturer, repacker, relabeler, or private label distributor were to add the lot number and expiration date to its bar code or add such information in a machine-readable format provided that the lot number and expiration date information is accurate. In a meeting with PhRMA on August 19, 2002, the industry representatives suggested to us that they might add machine-readable lot number and expiration date information if a demand existed for it. (We have placed a memorandum of this meeting in the docket for this rule, along with memoranda of meeting for other meetings we attended.) We do not know how much more such drugs would cost (compared to drugs that only had the NDC number encoded in the bar code) or whether hospitals and other health care facilities would be willing to pay more for drugs that have the NDC number, lot number, and expiration date in a bar code or machine-readable code, but the meeting raises the possibility that market forces could lead to the inclusion of lot numbers and expiration dates in bar codes or other machine-readable formats.

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

1. What Did We Hear from the Public Meeting?

In the public meeting notice, we asked whether we should require the use of a specific bar code symbology, such as reduced space symbology (RSS), adopt one symbology over another, or allow for ''machine readable'' formats (67 FR 41360 at 41361). We also asked for the ''pros and cons'' of each approach (id.). We had identified RSS as a possible symbology because we knew about industry-conducted pilot studies that used RSS bar codes on small vials (Ref. 35). Our reasoning was that if RSS symbology could be used on small containers, it could be used on larger containers, too.

The comments we received reflected an array of differing opinions, ranging from the adoption of a specific, non-bar code technology to prescribing no specific symbology or standard at all in order to promote innovation. Two principal, yet contradictory, themes emerged. One view advocated requiring a specific symbology or standard to promote uniformity and to create the conditions whereby hospitals could invest confidently in bar code scanning equipment, without having to buy different pieces of equipment to read different bar codes or other machine readable formats or without having to fear that any equipment purchases would soon become obsolete. Another comment declared that the bar code symbology adopted by FDA should be compatible with current scanning devices used by health care organizations. However, if the rule adopted a single symbology or standard, the rule could affect future innovation in this field, and we would have to engage in new rulemaking to adopt any newer symbology or standard.

The other view stated that we should not select any specific symbology or even require linear bar codes at all; instead, these comments said the rule should require the use of machine-readable or automatic identifier technology, thus creating the conditions under which newer, and perhaps better, technologies could be used in the future. However, the comments and our own analysis suggested that if the rule allowed for multiple symbol types or technologies, hospitals might be confronted with incompatible technologies and decide against buying multiple pieces of equipment. For example, if one drug used an RSS bar code, another used a radio frequency identification format, and a third used a unique, patented, automatic identification technology, a hospital would have to decide whether to buy a bar code scanner, a device to detect the radio frequency information, and a device to detect the patented identifier, or some combination of the three devices. If those costs were too great, the hospital could decide against making any equipment investments altogether, and the benefits from bar coding would not be realized.

Other comments suggested that we require the use of machine-readable codes capable of being read by ''machines currently deployed'' and ''economically available'' or use symbology that is ''compatible'' with ''current scanners.''

Some comments suggested that we conduct research to develop time lines for adopting specific bar code symbologies, that we have USP provide bar code standards, or adopt a standard or family of symbologies. Other comments said we should form a group involving various interests to study issues further or create an ''automatic identification coordinating council'' to ensure that minimum information requirements are met and that the best technology is used.

Deciding whether to require a specific symbology, standard, or an unspecified ''machine-readable'' symbol was a very difficult decision because of the comments' competing and sometimes incompatible positions. For guidance, we examined how another Federal agency reached a decision when confronted with an analogous problem of whether to require a particular action to accomplish a specific goal or to let market forces decide the outcome. We examined how the Federal Communications Commission (FCC) decided to adopt an order to require all television receivers to include digital television (DTV) reception capability in order to move towards a 2006 target date for a transition to digital television. Congress had imposed a December 31, 2006, target date for the return of the spectrum used by broadcasters for analog channels unless 85 percent of homes in a market could not receive local digital broadcast television signals. The FCC faced a problem; the public was reluctant to buy DTV receivers until there were DTV stations offering attractive DTV programs, but broadcasters lacked the incentive to provide such DTV programming in the absence of an audience that would attract advertisers (Ref. 36 at p. 13). Moreover, because analog televisions were still being sold, each sale of an analog television set put the FCC farther from reaching the 85 percent DTV reception goal (Refs. 37 and 38). The FCC ultimately decided to adopt a plan to require DTV tuners on almost all new television sets by 2007 and established a 5-year rollout schedule to minimize costs to television manufacturers and consumers. It recognized that requiring the manufacture of DTV receivers would address ''the root cause of the problem, namely the lack of television receivers capable of receiving DTV signals'' (Ref. 36 at p. 13). The FCC also recognized that, without its intervention, the transition to DTV might remain stalled. The FCC's decision to require all television receivers to include digital television (DTV) reception capability is

even more noteworthy because some FCC Commissioners did not favor significant regulatory intervention in the market (Ref. 38 at p. 1).

Our case is similar to the FCC's in the sense that we have an objective (reduction of medication errors) that can be achieved through bar codes, but hospitals are reluctant to invest in equipment because of the lack of bar coded products, and manufacturers, repackers, relabelers, and private label distributors are reluctant to invest in such bar codes or other technologies in the absence of a demand by hospitals or a requirement for such bar codes. If we fail to specify a particular measure, such as a symbology or standard, progress towards medication error reduction through bar codes could remain stalled; hospitals might still be reluctant to invest in equipment because of uncertainties in the marks, symbols, or technologies used on the drug or a limited amount of resources to buy different types of equipment to read the various marks, symbols, or other technologies. Likewise, manufacturers, repackers, relabelers, and private label distributors might not invest in bar codes or other technologies because no demand would exist or because their investments in such bar codes would be wasted if hospitals declined to buy the necessary equipment to take advantage of those bar codes or other technologies.

Consequently, proposed § 201.25(c)(1) would require the bar code for drugs and biological products (other than blood and blood products) to be any linear bar code in the UCC/EAN standard. This means that the bar code can be any linear bar code symbology, such as UCC/EAN–128, RSS, or UPC (if the UPC contains the NDC number), within the UCC/EAN standard. Adopting a linear bar code in the UCC/EAN standard, as opposed to a specific bar code symbology, should give firms some flexibility in selecting the bar code symbology that best fits their needs and should also give the rule some flexibility as linear bar code symbologies change, are added, or are phased out. For example, we know that the UCC has announced a ''sunrise'' date of 2005 for a new EAN–13 code because the commonly-used UPC code is running out of new company prefixes for that 12-digit code (Ref. 39). So, as new linear bar codes are added to the UCC/EAN standard, those new codes would be acceptable under the proposed rule as long as those new codes include the NDC number.

The UCC/EAN standard also has the advantage of being a widely used global standard. One comment submitted on behalf of the International Working Group on Barcoding of Pharmaceuticals advocated the use of the UCC/EAN standard because it represents a ''validated, testable global standard.'' The comment also suggested that regulatory authorities from Europe, Japan, and Canada are actively pursuing a bar code standard for pharmaceuticals and ''are watching to see what the FDA decides.'' Comments from the UCC, EAN, and some pharmaceutical interests also mentioned the global applicability of the UCC/EAN standard.

We recognize that other bar code standards exist, notably those advanced by the Health Industry Business Communication Council (HIBCC). HIBCC bar code symbologies include code 39 and code 128. (The UCC/EAN system also has a UCC/EAN–128 symbology that is similar, but not identical, to the HIBCC code 128.) HIBCC also has the Universal Product Number (UPN) system which is used for medical and surgical products. Comments from drug and biological product companies, however, usually referred to UCC/EAN standards if they identified any standard at all, so we presume that the use of UCC/EAN standards would be less disruptive to those industries compared to requiring the use of a different bar code standard. However, a comment from HIBCC suggested that some drugs may use HIBCC bar codes, that medical devices, in particular, are ''uniquely identified by the UPN number,'' and that the Department of Defense, Veterans Administration, and other organizations use the UPN numbering system. Therefore, we cannot preclude the possibility that some drug firms and organizations may use or prefer to use HIBCC bar codes, so we invite comment as to whether the rule should refer instead to linear bar codes without mentioning any particular standard or refer to UCC/EAN and HIBCC standards.

Our position presumes that, by the time any final bar code rule becomes effective (assuming that we do issue a final rule), bar code scanners will be able to read different UCC/EAN linear bar code symbologies reliably and efficiently. This is a critical consideration because the proposed rule's benefits are realized only if hospitals invest in bar code scanners, and we reiterate that their willingness to make that investment may depend on the number of different bar code symbologies that will be used and the ability of bar code scanners (particularly those scanners already in use at the hospitals) to read different symbologies. Comments from the public meeting disagreed on what capabilities different bar code scanning technology had to read different symbologies. Some comments suggested that new bar code scanners can read different linear bar code symbologies, particularly those in the UCC/EAN standard. In contrast, others suggested that bar code scanners may be unable to read newer bar code symbologies or that older scanners cannot read new symbologies or composite codes. Our understanding is that scanner capability depends on how the scanner is programmed (because scanners are programmed to read individual symbologies) and whether scanners can be upgraded or modified to read new symbologies. For example, some bar code scanners might be programmed to read the most commonly used linear bar codes and might not be able to read the RSS symbology. Some scanner manufacturers may be able to upgrade or modify an existing scanner to read newer symbologies, while other scanners, due to their age or the manner in which they were made, might not be capable of being upgraded. We invite further comment on this point.

As for non-bar code technologies, we know that other technologies exist or are under development, but we decline to specify the use of DataMatrix or other nonlinear bar code formats or technologies, such as radio frequency identification (RFID). We realize that other technologies may be able to encode more data or be more versatile compared to linear bar codes. For example, in a meeting with the National Alliance for Health Information Technology, we heard how RFID could be used to facilitate inventory control and to track individual items because each RFID tag would have its own unique ''electronic product code'' (EPC) consisting of a header code, an ''EPC manager'' that would probably identify the product's manufacturer, an ''object class'' that would refer to the product type, and a ''serial identifier'' that would be unique to each individual item. RFID's ability to track individual items could help drug companies and public health agencies identify and eliminate counterfeit drug products. However, the costs associated with RFID tags and readers could be significant; literature provided by the Auto-ID Center conceded that current RFID tags are ''fairly expensive'' and that a firm might have to purchase more than one reader if multiple RFID frequencies exist (Ref. 40). A representative from the Auto-ID Center stated that the ''target cost'' is five cents per RFID tag, so the technology could become more available and less expensive in the future.

Nevertheless, we find that linear bar codes are sufficient for encoding NDC

numbers, and hospitals that already have or intend to buy linear bar code scanners might not have to upgrade those scanners or purchase new devices if the proposed rule would require the use of linear bar codes only. In contrast, if we were to allow for other technologies such as RFID or even two-dimensional symbols such as DataMatrix, hospitals might have to buy RFID readers, optical scanning equipment, or other equipment because linear bar code scanners may be incapable of reading other technologies and, depending on the particular scanner, may be incapable of being upgraded. However, we invite comment on whether the rule should adopt a different format (whether that format is a symbology, standard, or other technology), and recommend that any comments advocating the use of a different model consider and discuss the following issues:

• What other symbol, standard, or technology should we consider, either in place of a linear bar code or in addition to it? How accepted is that symbol, standard, or technology among firms that would have to affix or use that symbol, standard, or technology? For example, we know that RFID technology has great potential for encoding a lot of data and for identifying individual products, but the technology is not yet widely accepted in the pharmaceutical industry due to its novelty and costs.

• Will hospitals be able to read or use the symbol, standard, or technology, either with existing equipment or equipment under development? We reiterate that hospitals might not have the financial resources to buy multiple pieces of equipment to read multiple, incompatible formats, so hospitals must be able to make equipment purchasing decisions confidently, knowing that they will recapture their investment costs.

Insofar as drug products are concerned, we also decline to have the proposal refer to the use of machine-readable codes or symbologies that can be read by machines ''currently'' used. Although a reference to ''machine-readable'' symbols or to ''current'' technology might seem to make a rule more accommodating to future technological developments, words such as ''machine-readable'' and ''current,'' when used in a regulation, can create several practical difficulties. For example, in the absence of an accepted standard or process, disputes could arise as to how we or any other person or group determines what is ''current.'' A manufacturer who wants to use a novel bar code or symbol could get different answers depending on whom it consulted; a hospital using linear bar code readers might find the novel code incapable of being read by its ''current'' scanners, whereas the firm marketing a new machine to read the novel code would argue that the novel code is ''machine-readable'' by ''current'' machines. Similarly, if only a fraction of the machines used in hospitals can read a new code, a hospital might argue that the new code cannot be read by ''current'' machines, yet, if machines were or could be upgraded or modified, a firm that marketed the machines or upgrade service might argue that the new code can, indeed, be read by current machines, provided that upgrades or modifications are made. These and other potential problems associated with a reference to ''current'' machines or ''machine-readable'' technology lead us to avoid using such terms in this proposal. (Different considerations apply for blood and blood products, and we discuss the proposed requirement for machine-readable symbols for blood and blood product containers at section II. H of this document.)

Furthermore, we decline to establish committees or other bodies to study the issue further or to decide technological issues. Given the comments we have received thus far, we have no assurance that a committee or other body would arrive at a consensus.

Nevertheless, if a group comprised of the affected industries and persons who would use the bar code could agree on a standard, symbology, or technology, we would be interested in learning about such standard, symbology, or technology and its costs and benefits. We would carefully review the information and consider the information when drafting a final rule.

2. Are There Any Specific Requirements for 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 to remain intact under normal conditions of use. These requirements would help ensure that the bar code can be read easily and accurately so that its safety benefits may be realized. We note that today some manufacturers have bar codes at locations where the bar codes are destroyed, damaged, or otherwise rendered useless. For example, some manufacturers have put bar codes on individual foil-wrapped packets, but the bar code overlaps the folds or perforations that separate the foil-wrapped packets. When one packet is separated from the others, the bar code is split into pieces, and the resulting bar code fragments can provide misleading or nonsensical information to the bar code scanner or might not be read at all by the scanner. So, the proposed rule would require the bar code to be placed in a manner so that it remains intact during normal conditions of use. For the foil-wrapped packet example, this would mean that the bar code would be placed away from folds or perforations so that each packet, when separated from the others, has its own intact and easily scanned bar code.

Note, too, that the proposal would include the phrase ''under normal conditions of use.'' Depending on the packaging and container used, the ''normal conditions of use'' may or may not require the bar code to remain intact at all times. For example, assume that you have a tablet in a blister package and that the bar code is printed on the flat side of the blister package. If the bar code is scanned before the tablet is pushed through the flat side, the bar code would not remain ''intact'' after the tablet has been dispensed, and this would be acceptable because, under ''normal conditions of use,'' the bar code would have already served its purpose by being scanned before the drug was dispensed. In contrast, assume that you have a bottle that contains multiple tablets. The bar code on the bottle, under proposed § 201.25(c)(1)(ii), would have to remain intact throughout the bottle's use so that the bar code could be scanned each time a tablet is dispensed from that bottle.

One comment said we should audit bar code quality, help industry build a bar code information infrastructure, publish our results, and support mandatory testing and verification of bar codes.

We decline to adopt the comment's suggestions. The bar code would be part of the drug's label, so issues concerning its quality and verification would be subject to current good manufacturing practices (GMP's). In general, persons who would be subject to the bar code requirement would be responsible for having written procedures for the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials, for exercising control over labeling materials and label operations, and for ensuring that correct labels are used (see 21 CFR 211.122, 211.125, 211.130). Failure to meet GMP's will cause a drug to be considered adulterated under section 502(a)(2)(B) of the act.

We also note that there are various standards relating to bar codes already. For example, the American Society for

Testing and Materials has a standard procedure for bar code verification (Ref. 41). The International Organization for Standardization has various standards for automatic identification and data capture techniques, and several deal with bar code quality and symbologies. The UCC has guidelines on bar code placement and other documents on specific symbologies or quality matters. Given these standards and other documents, as well as the comparatively greater expertise of standards organizations in this area, we do not intend to develop our own guidance documents regarding bar code details such as quality, verification, or testing.

The bar code can also be used to access the medication information found in the professional labeling of a specific drug product. We are currently working on a collaborative initiative 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 called the ''DailyMed.'' By linking the NDC to the appropriate label in the DailyMed, people will be able to use computer systems to access important medication information simply by scanning the bar code found on the drug package. This could help locate proper dosage instructions, identify drug interactions, and find other information necessary for the safe use of medications.

E. Where on the Label Would the Bar Code Appear? (Proposed § 201.25(c)(2))

In the public meeting notice, we asked where the bar code should be placed. We asked if there were benefits to placing bar codes on immediate containers and if there was a way to distinguish whether certain containers with a bar code would have a more significant effect on preventing medication errors than other containers (67 FR 41360 at 41361).

Some comments suggested that the bar code go on every package level down to the unit-of-use or unit dose. Other comments recommended placing the bar code on the ''immediate container'' or unit dose or unit-of-use package only.

In contrast, one comment expressed surprise that we would even consider putting bar codes on unit dose or unit-of-use packages because of the potential impact on manufacturers.

Several comments also disagreed as to whether we should specify where a bar code should appear on a particular package. For example, one comment recommended that we draft guidelines for bar code placement; the guidelines would consider ergonomics, scanner types, symbologies, and packaging. Another comment would require the bar code to be placed where ''the typical user of the scanning device can reliably and consistently scan it.''

In contrast, other comments stated that we should not restrict the bar code's placement on a package because differences relating to package size, shape, and material demand flexibility as to the bar code's placement.

Proposed § 201.25(c)(2) would require the bar code to appear on the drug's label. 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 requiring 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.

We decline to adopt the comments' positions to require bar codes on all packages or only on immediate containers because that would either result in too many products being bar coded or too few. For example, if we required every package to bear a bar code, then arguably a shipping container of drugs would have a bar code, even though no hospital would dispense a drug directly from a shipping container to a patient, and a bar code on the shipping container would have no impact on medication errors. (The bar code could help with inventory control and tracking, but such matters are outside the scope of this proposed rule.) If we required only the immediate container (which is the container that is in direct contact with the drug at all times) to have a bar code, then patients receiving multiple-unit containers (such as a box holding blister packed tablets) would be vulnerable to medication errors because the multiple-unit container would not have a bar code.

As the previous paragraph suggests, there may be more than one bar code on a product depending on the package and whether it has a unique NDC number. For example, assume that you make drug tablets that are individually packaged in a plastic blister pack and then boxed in a cardboard container. If the individually packaged tablets have a unique NDC number, then each individual blister pack would have a bar code. The cardboard container holding the blister pack would have to have a bar code, too, because the cardboard container would be an ''outer container'' within the statutory definition of ''label.''

Although proposed § 201.25(c)(2) would not require the bar code to appear at a specific location on a product, proposed § 201.25(c)(1)(ii) would require the bar code to remain intact under normal conditions of use. The latter requirement may influence the bar code's location.

F. What Would Happen if a Bar Code Could Not Be Put on a Product?

The proposed rule would not contain an exemption provision. We are aware of industry-conducted pilot studies that have placed RSS bar codes on small vials (Ref. 35). These pilot studies suggest that almost all products are capable of bearing a bar code. However, some comments from the public meeting suggested that small products might not be capable of bearing a bar code and recommended that we allow for exemptions.

We decline to create an exemption provision because we believe that almost all products are capable of bearing a bar code. In addition, exemption provisions sometimes create unintended administrative problems and consume agency resources as some individuals or firms may be tempted to submit exemption requests notwithstanding their ability to comply with a particular regulatory requirement. For example, if we were to create a general exemption provision, a firm whose drug product was packaged in a small vial might seek an exemption even though it could use a RSS linear bar code on that vial. If we tried to impose a limitation on the exemption, such as allowing for possible exemptions if it would not be technologically feasible to affix a bar code on the label, a firm might argue over whether economic or other considerations determined whether a bar code was technologically feasible. In the end, we could be obliged to devote resources to reviewing, deciding, and perhaps re-examining exemption requests, and we can avoid that potential drain on FDA resources by not creating an exemption provision. We invite comment as to whether any specific product or class of products should be exempt from a bar code requirement and the reasons why such an exemption is considered to be necessary. We also invite comment on

how we might create a waiver provision that would minimize the potential for misuse of the waiver. We will consider whether to incorporate specific exemptions into the rule.

G. What Is the Proposed Implementation Plan?

If we issue a final rule to require bar coding, we would require bar codes on human prescription drugs and OTC drugs dispensed under an order and commonly used in hospitals within three years after we publish the final rule in the **Federal Register**. The 3-year period would give affected parties time to obtain NDC numbers, if necessary, exhaust supplies of existing labels, and make new labels that contain the bar code or machine-readable information.

Additionally, because the bar code's addition to a label would be a ministerial act that would not require us to exercise any judgment as to the information being presented, we intend to have firms whose drug products are already approved or marketed notify us about the addition of the bar code to their product labels through an annual report (see § 314.81(b)(2)(iii) (21 CFR 314.81(b)(2)(iii) and 601.12(d)). For marketed OTC drugs, there is no comparable, routine reporting requirement if the drug is not the subject of an approved new drug application, and we do not intend to impose any reporting obligation relating to bar codes on OTC drugs.

We recognize that the bar codes' ability to prevent medication errors depends on many external factors outside this rule, such as the availability of bar code scanners, computer software that can process the bar code information and compare it against patient information, training health care professionals to use scanning equipment, and the willingness of hospitals to invest in bar code scanning equipment. However, requiring bar coding on human drugs is a necessary ''first step'' for promoting the use of technology to combat medication errors (Ref. 42).

We also acknowledge the various comments from the public meeting suggested different implementation periods for this rule. In general, some comments suggested short implementation dates measured in months whereas other comments suggested implementation dates measured in years. A few comments suggested different implementation dates for different products or would have the implementation date depend on the product's potential for harm. Several comments recommended requiring bar codes to contain the NDC number first, and require the lot number and expiration date at some future date.

We decided on the 3-year implementation date to give affected firms time to redesign their labels and exhaust pre-existing label stocks and to give hospitals time to decide which scanning devices or systems to develop or purchase. Additionally, as we suggested earlier, we want to give hospitals more time to decide whether they would be willing to work with pharmaceutical firms to have other information (such as lot number and expiration date) encoded. While we believe the 3-year implementation date is appropriate, we invite comment on whether the implementation period can and should be shortened.

We decline to create a ''phased-in'' implementation system whereby we would require the NDC number first, and then require inclusion of lot numbers and expiration dates at a future time. As we explained earlier in section II.C.2 of this document, we lack data that would support requiring lot numbers and expiration dates on bar codes at this time. While we will not object if firms volunteer to encode such information (assuming that they encode the correct information), we will not require or specify any implementation period for the encoding of lot number and expiration date information.

H. How Does This Rule Apply to Blood and Blood Components? (Proposed § 606.121(c)(13))

Like medication errors, errors involving blood transfusions can result in serious injury or death. For example, one study examined reported transfusion errors occurring between January 1, 1990, and December 31, 1999, from approximately 256 transfusion services in New York (Ref. 43). The study focused on reports involving the administration of a unit of blood to someone other than the intended patient or the issuance of incorrect blood because of a blood bank or phlebotomy error. During the study period, nine million red blood cell and whole-blood units were transfused, and 659 cases of erroneous administration were observed, for a frequency of 1 error per 14,000 transfusions. Five cases resulted in fatalities, at a rate of 1 per 1,800,000 units. In cases where the patient received an incompatible unit, nearly half (47 percent) suffered no ill effects, but 41 percent of the cases resulted in an acute hemolytic reaction, and 2 percent resulted in fatalities (id.) The most common error outside blood banks was administering properly labeled blood to a patient other than the one for whom the unit was intended (37 percent). In blood banks, the study identified issuance of the wrong unit (4 percent) and testing errors (7 percent) as some common errors (id.).

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 reference to ''machine-readable symbols'' in § 606.121(c)(13) was intended to be flexible and accommodate changes in machine-readable technologies. For example, FDA recognized the use of Codabar (a specific bar code symbology) in 1985, and, in 2000, approved the use of ISBT 128, version 1.2.0 (Ref. 44).

Unlike the situation for other prescription drugs, there is already substantial use of bar codes for blood and blood products. Most blood establishments currently use machine-readable symbols or ''ABC Codabar'' on their blood and blood component labels. In August, 1989, the International Society for Blood Transfusion (ISBT), an organization established to promote and maintain a high level of ethical, medical, and scientific standards in blood transfusion medicine and science throughout the world, recognized that ABC Codabar, the first bar coding system adopted by the health care industry, was becoming outdated and initiated the design of a new system using the bar code symbology which eventually became known as ISBT 128.

In December, 1996, the International Council for Commonality in Blood Bank Automation (ICCBBA) held an ISBT 128 Consensus Conference in Washington, DC, to provide an opportunity for dialogue among the affected industry groups and FDA. Although there was a consensus for use of ISBT 128, some participants expressed concerns regarding implementation time frames and costs of implementation to hospital transfusion services. However, ISBT 128 has numerous advantages over the ABC Codabar. For example, ISBT 128 is more secure, allows more flexibility in coding highly variable information, uses double-density coding to allow more information to be encoded in a limited space, and can be interpreted by the same bar code readers used with ABC Codabar.

The ISBT 128 bar code system established by ISBT is similar, but not identical to, Code 128. ISBT 128 is a copyrighted symbology. The ability to read, store, interpret, transfer, print, or otherwise manipulate ISBT 128 data structures requires registration with the ICCBBA and payment of an annual

licensing fee, and the ICCBBA uses the fees to revise, enhance, extend, and maintain the ISBT 128 system and associated databases (Ref. 45). The ISBT Council accepted an application specification for ISBT 128 in July, 1994, and approved a resolution that all bar coded blood products collected after July 4, 1998, be labeled using ISBT 128. However, the use of ISBT 128 in the United States has been slow, and the ISBT 128 system has not been implemented in accordance with the ISBT Council's resolution.

Despite the international convention and guidance document, comments submitted in response to the public meeting suggest that § 606.121(c)(13) has not resulted in a uniform, international bar coding system for blood in the United States. While some comments described ISBT 128 in favorable terms, stating, for example, that it allows more information to be encoded or is more accurate than Codabar or that ISBT 128 represents an internationally-accepted standard for blood, at least one comment indicated that licensing fees associated with ISBT 128 may deter hospitals from using the ICCBBA system. Comments were also divided as to whether to require the use of ISBT 128 or simply require the use of ''machine readable'' symbols.

We considered whether the proposal 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. Each approach has its advantages and disadvantages. For example, requiring the use of ISBT 128 would help ensure a uniform bar coding standard for blood and blood components and be consistent with the international standard, but requiring ISBT 128 would mean that we would have to institute new rulemaking if a new symbology, standard, or technology was adopted. Requiring ''machine-readable'' information approved by the Director of CBER would allow CBER to consider new technologies in the future, but could result in some blood establishments adopting one system and others using a different system, thereby defeating the goal of creating a uniform system for identifying blood and blood components. Therefore, we invite comment as to whether we should require the use of ISBT 128, require the use of a symbology consistent with that required for drugs in proposed § 201.25, or require ''machine-readable information'' as approved by the Director of CBER or some other standard or symbology.

In developing this proposal, we recognize that the blood industry currently uses a machine-readable code that does not meet UCC/EAN standards. Some comments at the public meeting stated that the scanners are capable of reading multiple systems (e.g., UCC/EAN and ISBT). Based on our understanding of the state of the industry and the ability of scanners to read more than one symbology, we decided to propose a rule that would permit the existing coding to continue. We invite comments on whether this proposal is feasible or whether we should require the use of UCC/EAN standards for blood and blood components.

The proposal would require that the machine-readable information meet certain minimum requirements and be approved by the Director of CBER. These minimum requirements would move us closer to the goal of increasing patient safety. We anticipate that the industry will standardize encoded machine-readable information and readers, using our minimum requirements to minimize, to the greatest extent possible, the need for ''country-specific'' software and the high cost associated with software development and maintenance.

Thus, we propose to amend § 606.121(c)(13) to require the use of ''machine-readable information'' approved by the Director of CBER. The Director will 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 Public Health Service Act are subject to the machine-readable information requirement. This would be consistent with the pre-existing requirement at § 606.121(a) and (b).
- State that blood and blood components intended for transfusion are subject to the machine-readable information requirement. This would be consistent with the pre-existing requirement at § 606.121(a) that describes the purpose behind container label requirements.
- 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. This would reflect the pre-existing requirement at § 606.121(c)(1), (c)(2), (c)(3), (c)(10), and (c)(12).
- 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. This would be consistent with the pre-existing requirement at § 606.120(c) that requires labeling to be clear and legible.
- 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. To illustrate how this would work, the proposal's reference to any blood or blood component would include a unit of whole blood, packed red blood cells, plasma, platelets, and cryoprecipitate AHF. The unit of blood or blood component label would contain the machine-readable information if the blood or blood component has any possibility of being transfused to a patient, whether or not the unit is actually transfused. Additionally, the phrase, ''from which the blood or blood component can be taken and transfused to a patient'' would include the circumstance where blood or a blood component is extracted or aspirated with a syringe from the container of blood or blood component in order to transfuse to a patient. This technique might be used when transfusing neonates or under other medically necessitated circumstances. In this case, the blood or blood component from which the aspirate is taken must have affixed to it a label containing the required machine-readable information. This would be consistent with the pre-existing requirement at § 606.121(c)(8)(iii) that requires specific statements if a product is intended for transfusion.

We also invite comment on how the proposed rule might affect hospitals where patients receive blood or blood components. Specifically, we want to hear how the proposal might affect a hospital's decision to purchase a machine reader (e.g., scanner) that properly identifies the intended recipient of the blood or blood component. To prevent medical errors, this machine reader would need to be compatible with the machine readable information encoded on the blood or blood component label, yet a hospital's purchasing decision might also be influenced by the bar codes appearing

on drugs and OTC drugs that are dispensed pursuant to an order and commonly used in the hospital.

We intend to make a machine-readable information requirement effective for blood and blood components 3 years after we publish a final rule in the **Federal Register**. Changes to existing blood and blood component labels would require the submission of an annual report as described in 21 CFR 601.12(f)(3).

I. What Bar Code Requirement Would Apply to Biological Products? (Proposed § 610.67)

The proposal would create a new § 610.67 that describes a new labeling requirement for biological products (other than blood and blood products, which would be covered by proposed § 606.121(c)(13)). Proposed § 610.67 would simply state that biological products must be labeled in accordance with the bar code requirements at § 201.25. In addition to the separate authority provided by section 351(j) of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act also applies to a biological product that is regulated under section 351 of the Public Health Service Act.

The proposal would not apply to biological products that are regulated as devices for the reasons we stated earlier in section II.B.2.d of this document.

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)) (21 U.S.C. 321(n), 321(p), 351, 352, 353, 355, and 371(a)) of the act, and sections 351 and 361 of the Public Health Services Act.

A bar coding requirement for drugs 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 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 the drugs (prescription drugs and the subset of covered OTC drugs) covered by this proposal may be used in the hospital setting, such use in hospitals can be considered the ''conditions of use as are customary or usual.'' As is made clear in section I of this document, 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 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 will ensure the safe and effective use of drugs by reducing the number of medication errors in hospitals and other health care settings. Such 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.

Section 505(b)(1)(D) of the act requires a new drug application 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 section 351(a)(2)(B)(i)(II) of the Public Health Service 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 this document, 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 repackaging. A bar coding requirement therefore prevents 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 this 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 biological products, including blood, are also prescription drug products, the sections of the act discussed elsewhere in this legal authority section provide ample legal authority for promulgating a regulation requiring bar coding for such biological products. There is, however, additional legal authority for the rule's requirements as to biological products. Section 351 of the Public Health Service Act authorizes the imposition of restrictions through regulations ''designed to insure the continued safety, purity, and potency'' (including effectiveness) of the products. Biological product licenses are to be ''issued, suspended, and revoked as prescribed by regulations'' (42 U.S.C. 262(d)(1); see §§ 601.4 through 601.6). The bar code requirement for biological drugs, and the machine-readable information requirement for blood and blood products, is designed to insure the continued safe and effective use of licensed biological products. Therefore, if this rule were finalized, we may refuse to approve biologics license applications (BLAs), or may revoke already approved licenses, for biological drug products that do not have such codes.

Additionally, section 361 of the Public Health Service Act authorizes regulations necessary to prevent the introduction, transmission, or spread of communicable diseases. With specific regard to blood and blood products, the requirement for machine readable information will aid in the recall, quarantine and retrieval 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 seizure, injunction, and prosecution, and violation may result in withdrawal of an NDA or BLA.

IV. Environmental Impact

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

V. Paperwork Reduction Act of 1995

This proposed 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 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.

We invite comments on: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Bar Code Label Requirement for Human Drug Products and Blood.

Description: We are proposing a new rule that would require human drug product and biological product labels to have bar codes. The proposed rule would require bar codes on human prescription drug products and OTC drug products that are dispensed pursuant to an order and commonly used in hospitals and would require 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 hospitals, the bar code would contain the National Drug Code for the product. For blood and blood components, the proposed rule would specify the minimum contents of the machine-readable information approved by the Director of the Center for Biologics Evaluation and Research as blood centers have generally agreed upon the information to be encoded on the label. The proposed rule would 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 the Center for Drug Evaluation and Research would have bar code information for drugs subject to a new drug application or abbreviated new drug application to be reported through an annual report, this proposed rule affects the reporting burden associated with § 314.81(b)(2)(iii) (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 products 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 product 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 0910–3338. 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).

Description of Respondents: Persons who manufacture, repackage, or relabel prescription drug products or OTC drugs that are dispensed pursuant to an order and commonly used in hospitals, and blood establishments.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Frequency of Responses	Total Annual Responses	Hours per Response	Total Hours
§ 201.25, § 610.67	1,447	31.1	45,000	24 hrs.	1,080,000
§ 314.81(b)(2)(iii)	1,447	5.9	8,576	10.5 min.	1,497
§ 601.12(f)(3)	211	1	211	1 min.	3.5
§ 606.121(c)(13)	981	42,507.7	41.7 million	1 min.	695,000
Total					1,776,590.5

[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 (including prescription biologics and vaccines) and OTC drugs subject to the bar code requirement, information from our own records indicates that there are 1,447 establishments that would be affected by a bar code requirement, and there are approximately 89,800 separate, identifiable product packages subject to this proposed rule. We expect that half of the packages (45,000) would need redesigned labels to comply with a bar code requirement because they do not currently use coded NDC numbers. This means that the annual frequency of reports, under proposed § 201.25 (and proposed § 610.67 for biological products not regulated as devices), would be 31.1 (45,000 package labels requiring a bar code/1,447 establishments = 31.09 packages per establishment, which we have rounded up to 31.1). Consultations with industry sources suggest that the number of hours per response to redesign a package label to include bar coded information to comply with this regulation is approximately 24 hours. Therefore, the total burden hours for proposed § 201.25 and § 610.67 would be 1,080,000 hours (45,000 packages x 24 hours per package label = 1,080,000 hours).

• For prescription drugs whose label changes would be reported in an annual report under § 314.81 or under § 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 proposed 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 blood and blood component manufacturers. 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 proposed § 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 American Association of Blood Banks 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 three 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 1 minute to apply a machine-readable code manually; if a blood collection facility uses an on-demand printer, the time would range between 15 to 30 seconds. For purposes of this estimate, we adopt the larger time estimate of 1 minute per machine-readable information for blood, thus resulting in an annual reporting burden of 695,000 hours ((41.7 million reports x one 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.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), we have submitted the information collection requirements of this rule to OMB for review. Interested persons are requested to fax comments regarding information collection by April 14, 2003, to the Office of Information and Regulatory Affairs, OMB (see **ADDRESSES**).

VI. Executive Order 13132: Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between 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 order and, consequently, a federalism summary impact statement is not required.

VII. Analysis of Impacts

A. Introduction

We have examined the proposed 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 proposed rule is consistent with the principles set forth in Executive Order 12866 and the three statutes. We have identified the proposed rule as an economically significant regulatory action, as defined in Executive Order 12866. We believe the proposed rule is unlikely to have a significant impact on a substantial number of small entities. The expected cost of this proposed rule 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 proposed rule to be major under the Congressional Review Act.

We contracted with the Eastern Research Group, Inc. (ERG), to collect data, interview industry experts, and analyze the costs and benefits of the proposed rule. The detailed analyses and references in support of the impacts summarized in Table 2 are included in the docket as Reference 46.

TABLE 2.—ESTIMATED IMPACTS OF THE PROPOSED RULE (IN MILLIONS OF DOLLARS) (OVER 20-YEAR PERIOD AT 7-PERCENT DISCOUNT RATE)

Impacts	Regulatory Costs	Anticipated Hospital Costs[1]	Societal Benefits[2]	Potential Hospital Efficiencies[3]	Net Benefits (benefits minus costs)[4]
Present Value	$53.1	$7,204.3	$41,381.3	$4,783.3–$7,643.0	$34,123.9
Annualized	$5.1	$680.0	$3,906.1	$451.5–$721.5	$3,221.0

[1] Costs due to voluntary accelerated purchase and utilization of bar coding systems.
[2] Benefits to public health due to avoidance of adverse drug events.
[3] Potential efficiencies in reports, records, inventory, and other hospital activities.
[4] Net benefits include only public health benefits of increased patient safety.

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 health care sector. These investment expenditures are necessary to achieve the societal benefits expected from the proposed 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 societal benefits would occur after hospitals purchase and install the necessary equipment to take advantage of bar codes. The net benefit figure is the societal benefit minus the induced expenditures minus the regulatory costs. This estimate, however, accounts for neither potential hospital efficiencies, nor income transfers to hospitals following fewer awards for medical malpractice.

B. Objective of the Proposed Rule

The objective of the proposed rule is to enable the health care sector to utilize technological solutions to reduce preventable adverse drug events (ADEs)[2] associated with medication errors[3] in hospitals.[4]

C. Estimate of Risk/Risk Assessment

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 the agency's efforts to estimate the current number of preventable ADEs.

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.

ERG identified four comparable published studies that reported rates of ADEs per hospital admissions (Bates et al., 1995, Classen et al., 1997, Jha et al.,

[2] 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 Hospital Pharmacists, 1998)

[3] 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)

[4] 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)

1998, and Senst et al., 2001). 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 nonobstetric hospital admissions during 2000. 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 372,400 (30 percent) of these ADEs were preventable. Based on published reports (Bates et al., 1998, and Leape et al., 1998), we also estimated that 1,046,000 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 ADEs could triple 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 as many as 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 have resulted in permanent disability. We used these estimates in our analysis.

D. The Proposed Rule

We propose to require machine-readable information on all prescription drug and biological products (including vaccines), all OTC drug products dispensed pursuant to an order and commonly used in hospitals, and all human blood products. This information would include the NDC number identifying the dosage, strength, nature, and form of each administered product and would be portrayed in a standardized linear bar code[6] and include product-specific and package-specific NDC numbers. We would 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, if finalized, be effective within 3 years after we have published a final rule.

We are proposing this regulation 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 reduce the number of ADEs 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 proposed rule would increase costs to the manufacturers, marketers, and packagers of the affected products by requiring changes in manufacturing, packaging, and labeling processes. It would also increase costs to some hospitals by requiring a change in some bar code readers associated with these products. The proposed rule would 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 proposed rule would enable hospitals to take advantage of the coded information that would permit hospitals to reduce ADEs, while achieving other operational cost efficiencies. The proposed rule would 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).

E. Description of Affected Sectors

1. Current Machine-Readable Technologies

Before developing the proposed 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. 47) 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. Healthcare 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 Bar Code 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 the HIBCC code has been more effectively used by medical device manufacturers, it has not won wide acceptance within the 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 symbology). 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 that would be required by this proposed 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 their 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 nonwater soluble inks produce a shine that reflects to the scanner and affect how the bar code is read. Laser printers are subject to toner

[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.

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

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 wards due to their portability and multi-functional characteristics.

2. Manufacturers and Packagers of Affected Products

Discussions with staff at two large Veteran Health Administration Comprehensive Mail Order Pharmacies indicate that the large majority of exterior pharmaceutical packages include the NDC number in a bar code. The proposed rule, however, would require this bar coded information on both exterior and interior packaging. In addition, some prescription and OTC drug products are 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 rarely include bar coded information on blisters. 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.

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

There are currently approximately 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 approximately 3,728 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 501 packaging lines. Overall, we estimate that 4,229 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 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 4,995 affected packaging lines in 2,428 separate establishments.

The number of separate trade and generic named products has increased by over 500 percent since 1990, and now encompasses about 17,000 names. Each of these named products may be marketed in varying strengths or dosage forms. Overall, we estimate 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 fewer than 10 percent of OTC packages (9,800 packages) are commonly used in hospital settings and would be subject to the proposed rule. For example, OTC analgesics that may be dispensed to a patient pursuant to an order would be subject to the proposed rule, but mouth rinses or toothpastes that may be provided would not. We are collecting data to confirm the proportion of affected OTC drug products. The Consumer Healthcare Products Association (CHPA) estimated that as many as 10 percent of their members' 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 drug products are routinely dispensed. For purposes of this analysis, we have assumed that 10 percent of all OTC drug products would be required to provide bar coded information. We are trying to collect better information for these products. Overall, 89,800 separate unit-of-sale packages are expected to be subject to the proposed rule.

OTC drug manufacturers frequently redesign labels. Based on discussions with manufacturers, we believe that 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. While marketing of prescription products may not be as sensitive to labeling graphics and package design as OTC products, there are many other reasons why manufacturers change their labels. Although we examined NDA files and found that changes to prescription product labels occur an average of more than once per year, for this analysis we have nevertheless assumed that the proposed rule would require significant involuntary actions by the affected industry.

3. Retail Outlets

Retail pharmacies currently have the capacity to read linear standardized bar codes at their in-house scanners. However, if we had selected an alternative to the proposed rule that would have required reduced space symbology (RSS), the current stock of scanners may have required upgrades or replacement. These upgrades would not have been directly mandated by 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 a single standard would not require scanner replacements or upgrades. Only OTC drug products dispensed pursuant to an order and commonly used in hospitals would be affected by the proposed rule. 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. 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 proposed rule is not expected to impact this sector, but we have considered alternatives that would affect retail outlets.

4. Hospitals

The proposed rule would not require hospitals to introduce the new automated technologies, but the development of consistent bar codes on

pharmaceutical and blood products would 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 might necessitate the use of RSS symbology. In order to scan these products properly, hospitals that currently have installed bar code readers may need to upgrade or replace some scanners. According to the most recent census, there are 6,591 hospitals in the United States (NAICS 622) with a total of over 1.25 million beds. Estimates of personnel in these hospitals include 97,500 pharmacists, 75,500 pharmacy assistants, and almost 1.2 million nurses. Overall, a nurse is responsible for 4.5 beds per shift. An average hospital includes 191 beds and employs approximately 15 pharmacists, 11 pharmacy assistants, and 182 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 one percent of all hospitals have installed bedside, point-of-care systems that use bar coded information. An additional three percent of hospitals use some form of computerized system in the medication process, but not all use bar codes. Overall, an estimated two percent of all hospitals (131 hospitals) currently use bar codes in everyday operations. Even in the absence of the proposed rule, we expect the remaining 6,460 hospitals to gradually implement computerized tracking systems. Discussions with industry consultants and the American Hospital Association (AHA), however, suggest that without standardization, it would take 20 years for all hospitals to adopt and use systems with bar code readers and utilize 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, these industry experts felt that 20 years was a reasonable expectation. We examined the impact of alternative acceptance streams as a sensitivity analysis.

We requested comments on the potential uses of bar coded information on drug products at a public meeting held on July 26, 2002. These comments 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 avoidance. While some of these returns to hospitals (such as reduced liability awards and malpractice liability insurance premiums) may be transfers, we believe additional efficiencies are likely.

5. FDA Oversight and Responsibilities

We would be affected in two 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.

The second area in which our activities would be impacted by the proposed rule is our use of compliance resources. The proposed rule would require the affected products to have bar coded information. Although the exact impact on our compliance resources is not quantified, we recognize that the creation of new regulatory requirements would require additional resources to ensure compliance.

F. Regulatory Costs of the Proposed Rule

1. Introduction

We estimated costs for a 20-year evaluation period to reflect the time that hospitals are expected to 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 in the affected sectors over the entire evaluation period using a seven percent annual discount rate. We assume that costs accrue at the beginning of any period. The detailed calculations and references that support the following analysis are available in Reference 46.

2. Costs to Manufacturers and Packagers of Affected Products

The pharmaceutical industry would face compliance costs from this proposed rule because we would require manufacturers, repackers, relabelers, and private label distributors to include NDC numbers in bar code format, using linear standardized symbology, down to the unit-dose level. The proposed rule would require this information within 3 years of the implementation date of the final regulation. The proposed rule would also affect the production processes of the pharmaceutical and biological product industries. Although manufacturers appear to initiate labeling changes fairly often for internal purposes, the proposed rule would necessitate 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 $26.3 million over the first 3 years of the evaluation period. Most costs ($17.6 million) accrue for modifications to unit-dose interior packaging to include a unique NDC number in a linear standardized format for every product. Exterior packaging modifications that include NDC information would cost $4.1 million over the 3-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 $3.8 million over the 11th, 12th, and 13th evaluation year for this replacement and upgrade. In addition, the packaging production process would require additional annual operating and maintenance costs reaching $0.4 million by the third evaluation year. In total, we estimate that the PV of the costs incurred by prescription drug manufacturers, repackers, and relabelers to comply with the proposed rule over the 20-year period is $30.4 million and the annualized cost is $2.9 million.

b. *Over-the-Counter Drugs*. The OTC drug industry has estimated that fewer than 10 percent of its products are commonly used in hospitals (CHPA, 2002). We are currently collecting data on the size of this market share. For this analysis, we assume that 10 percent of all OTC drug products would be subject to the regulation and will include bar coded NDC numbers. The industry would either assign internal production processes that allow labeling differentiation for these products, or repackers and relabelers would provide the required labeling. We believe that

the magnitude of packaging changes required to install bar coding equipment 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 $1.7 million over 3 years, with additional capital investments of $0.1 million during the 11th evaluation year. The estimated annual operating costs to provide bar codes to the affected proportion of the OTC drug market are negligible (less than $0.05 million by the third year). Overall, the PV of these costs over the 20-year evaluation period to the OTC drug industry is $2.1 million and the estimated annualized costs are $0.2 million.

c. *Blood and Blood Products*. Manufacturers of blood and blood products would also be affected by the proposed rule. Although most blood and blood product manufacturers have voluntarily applied bar coded information, this requirement would add to their costs by requiring specific machine-readable information in a consistent format. These costs would equal approximately $0.4 million over the first 3 years, with additional capital expenditures of $0.1 million over the following 20-year evaluation period for replacement or upgrade of equipment installed in response to the proposed rule. The annual operating costs to blood manufacturers of maintaining the equipment would be negligible (less than $0.05 million by the third year). We estimate that the PV of these compliance costs to blood and blood product manufacturers for using machine-readable information in a consistent machine-readable format over the 20-year period is $0.7 million and that the annualized costs are $0.1 million.

d. *Total Cost to Manufacturers, Repackers, and Relabelers*. The estimated PV of regulatory costs to manufacturers, repackers, and relabelers of prescription drug products, OTC drug products, blood, and blood products is $33.2 million. The average annualized costs to these industries are $3.2 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 linear bar codes described in the proposed rule. However, if we had selected an alternative that would have required 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 would not be affected by the proposed rule.

4. Costs to Hospitals

The proposed rule would require NDA numbers in linear bar codes on the immediate containers of affected products and machine-readable information on blood and blood products. However, because manufacturers, repackers, and relabelers are expected to find it necessary to use RSS symbology on small unit-dose packages or vials and bottles, their scanners and readers must have the ability to capture this information in a RSS format. As a result, in order for hospitals that have currently installed bar code reading systems to maintain current operating practice, their scanners may need to be replaced with scanners that are capable of reading RSS symbologies. Replacement of these scanners would not be a voluntary hospital investment, but would be necessary to maintain current operations.

These costs are somewhat mitigated for the approximately 2 percent of all hospitals (131 hospitals) that currently use 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 apply bar codes on nearly 28 percent of dispensed medications. These 131 hospitals would avoid these expenditures under the proposed rule.

The proposed rule would result in the premature replacement of scanners used in hospital pharmacies and treatment wards. ERG has estimated that the PV of the incremental initial cost of accelerated scanner replacement or upgrade to read RSS symbologies, based on the expected remaining useful life of current equipment, is approximately $13.7 million. The average annualized costs to hospitals of early replacement is $1.3 million.

According to reports in the literature, it costs as much as $0.03 per unit-dose to apply a bar code in hospital pharmacies. Avoidance of this activity will reduce costs by approximately $0.7 million per year. The PV of this cost reduction is $7.6 million.

Overall, we estimate the PV of regulatory costs, less the cost savings to hospitals of the proposed rule, to be $6.1 million, and the average annualized costs are $0.6 million.

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 89,800 of these packaging units would need bar coded NDC numbers because we estimate that only 10 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 449,000 new NDC codes over 20 years, or 22,500 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 data base containing all NDC numbers. This implies an annual resource requirement of 11,250 hours, or approximately 5.6 full-time equivalents (FTEs). These direct resources require supervision, administration, and support. To account for these indirect resources, we multiplied direct resources by two, resulting in 11.2 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 $1.3 million with a PV of $13.8 million. Although additional regulatory requirements, such as requiring readable bar code information on product labels, would increase our compliance burden, we have not quantified that impact at this time.

6. Total Regulatory Costs

The estimated PV of the total direct regulatory costs of the proposed rule over the 20-year period is $53.1 million, which is equivalent to an annualized cost of $5.1 million. Table 3 illustrates the timing of the stream of investments and increased annual operating and maintenance costs expected from the proposed rule.

TABLE 3.—REGULATORY COSTS (IN MILLIONS) BY YEAR

Evaluation Year	Investment During Year	Operating and Maintenance Cost
1	$23.2	$0.9
2	$9.5	$1.0
3	$9.5	$1.1
4	0	$1.1
5	0	$1.1
6	0	$1.1
7	0	$1.1
8	0	$1.1
9	0	$1.1
10	0	$1.1
11	$1.4	$1.1
12	$1.4	$1.1
13	$1.4	$1.1
14	0	$1.1
15	0	$1.1
16	0	$1.1
17	0	$1.1
18	0	$1.1
19	0	$1.1
20	0	$1.1

G. Other Anticipated Expenditures

We anticipate that the proposed rule would affect all facilities defined as hospitals and included in NAICS 622, including general medical and surgical hospitals, psychiatric and substance abuse hospitals, and other specialty hospitals. We did not quantify impacts on nursing and residential care facilities (NAICS 623). The proposed rule would impact hospitals by encouraging them to accelerate the efficient use of bar code reading technology in hospital bedside point of care settings. The expected increased investment would lead to a significant reduction in the number of ADEs among hospital patients. We assume that investments by the health care sector are made at the beginning of each period.

The hospital sector has long considered the application of bar code reading technology for its facilities. According to the AHA, almost half of the hospitals in the United States have explored the possibility of independently installing this technology. A few (about four percent of all 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 only applicable 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 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.

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 installation of scanners, readers, software, initial training etc. is $377,000.[9] In addition, although there is considerable uncertainty, ERG contacted hospital industry executives and consultants who agreed that negative productivity effects were likely after installation of a bar code reading system. The contacts noted that using the scanners could result in reductions in patient ward productivity because current scanners and administration procedures would have to be revised to accommodate this technology. Difficulties could arise, for example, when multiple doses of medication are required at the same time for different patients and 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, but our analysis assumes that hospital ward productivity levels would fall by three percent annually over the evaluation period. The annual opportunity costs of these productivity losses, together with the operation and maintenance expenses, amount to $320,000 per year for the average sized hospital. Some of these expected productivity losses would be mitigated by efficiency gains in other hospital procedures and are 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 in the absence of this proposed rule, the hospital sector would likely install bar code readable technology within 20 years. Therefore, we believe that, while approximately 131 hospitals currently use bar codes in everyday operations, the remaining 6,460 hospitals would ultimately invest in this technology. The experts have also predicted 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 make these investments much earlier. For example, ERG estimated that if in-hospital pharmacy operations were no longer required to repackage and relabel products because of the proposed rule, the annual operating and maintenance costs of a bar code scanning system would fall from $377,000 to $314.800. Thus, we believe that the proposed rule would effectively prompt facilities to accelerate these investments.

[9] Per hospital expenditures and benefits are based on an average sized hospital based on bed capacity. The average United States hospital has 191 beds (ASHP, 1999).

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 would be 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 five 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 a regulation. We acknowledge that precise estimates of the rate of acceleration of technology acceptance are highly uncertain, but industry experts have indicated that doubling the rate of technology acceptance is a reasonable assumption. Alternative rates of acceptance were analyzed and discussed as a sensitivity exercise. We specifically invite public comment on the feasibility of this assumption.

ERG used a Probit function to estimate the annual rate of acceptance. This function assumes a normal density distribution for the selected period and has been used to describe rates of technology acceptance for other new products. Consequently, over 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 $7.2 billion. The estimated annualized cost is $680.0 million. Table 4 shows the expected annual incremental expenditures by year for adopting hospitals under the proposed rule.

TABLE 4.—EXPECTED INCREMENTAL HOSPITAL EXPENDITURES (IN MILLIONS) PER YEAR[1]

Evaluation Year	Incremental Cost to Hospitals Adopting Bar Codes[1]
1	$1.2
2	$18.9
3	$129.8
4	$506.9
5	$1,187.4
6	$1,823.6
7	$2,062.7
8	$1,934.0
9	$1,617.8
10	$1,226.8
11	$834.3
12	$499.2
13	$254.5
14	$102.4
15	($15.3)[2]
16	($29.4)
17	($34.5)
18	($35.6)
19	($36.0)
20	($36.0)

[1] Reflects both negative and direct positive fixed productivity changes. Hospitals expected to install bar code systems without the proposed rule would not achieve productivity gains associated with internal repackaging. Therefore, given the different expected rates of technology adoption with the proposed rule, the hospital sector would have net productivity gains beginning in the 15th evaluation year.

[2] Numbers in parentheses indicate cost reductions from baseline.

H. Reduction in Preventable Adverse Drug Events

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

ERG determined that, under current conditions, about 1.25 million ADEs occur each year in the United States, of which 372,400 are preventable. As discussed above, the proposed rule 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 (Malcolm et al., 1999; Yang et al., 2001; Brown, 2002; Rough, 2002; and Churchill, 2002). 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 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 times 0.5), which would prevent about 84,200 ADEs per year (372,400 times 0.226). This equals a reduction of 12.8 preventable ADEs per year for an average hospital. We believe the assumption that bar code readers could intercept one-half of both dispensing and administration errors is reasonable and conservative, but we specifically invite comment on alternative interception rates. This assumption is tested as a sensitivity analysis.

We estimate that the proposed rule, by stimulating earlier hospital investment in bar code scanning systems, would produce a corresponding increase in the number of avoided ADEs. To project the aggregate number of ADEs avoided due to the proposed rule, ERG calculated the number of ADEs 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 3,295 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 would intercept an estimated 42,182 errors (12.8 ADEs per hospital times 3,295 hospitals) that would otherwise have resulted in ADEs during that year. Over the entire evaluation period, this methodology predicts that the accelerated investment would avoid over 413,000 ADEs.

I. Value of Avoided ADEs

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 (Classen et al., 1997; Bates et al., 1997; and Senst et al., 2001). 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 one 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 (one minus 0.95) times 0.005, or 0.0003 QALYs. There are no precise means of valuing QALYs. One approach is to derive the value from studies that estimate the willingness-to-pay to avoid a statistical death. For example, values derived from occupational wage-premiums to accept measurable work-place risk suggest a figure of about $5 million per statistical death avoided. Apportioning this value over the remaining life expectancy of the average workforce member and adjusting for future disability implies (at a 7-percent discount rate) a value per QALY of about $373,000. Thus, in the example above, the value of the decease in QALYs due to minor drug toxicity would be $102.

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) result 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 $181,600. We note that this value is very sensitive to the number of fatal preventable ADEs.

J. Aggregate Benefit of Avoiding ADEs

FDA and ERG estimated the benefit of avoiding ADEs due to the use of bar code reading systems by multiplying the value of each avoided preventable ADE by the expected number of ADEs avoided. As stated earlier, an average hospital is expected to have 12.8 fewer preventable ADEs each year after installing bar code reading technology. The direct cost savings by avoiding treatment ($2,257 per ADE) and the weighted preference value ($181,600 per ADE) indicate a societal value of $183,900 per average ADE avoided, and a societal benefit of about $2.35 million per facility per year. We multiplied this derived value per hospital by the expected difference in the number of hospitals with installed bar code technology under the proposed rule. For example, during the 10th evaluation year, an estimated 3,245 additional hospitals would have installed bar code reading systems due to the proposed rule. We would expect the increased use of these systems to result in 42,182 fewer ADEs. The estimated PV of avoiding these ADEs is $7.7 billion. The PV of the societal benefits that would result from reductions in ADEs over the entire 20- evaluation period is $41.4 billion. The annualized societal benefit of the reduced number of ADEs is $3.9 billion. Table 5 illustrates the expected reduction in ADEs for the entire evaluation period.

TABLE 5.—EXPECTED REDUCTION IN ADEs BY YEAR WITH BAR CODE (SOCIETAL BENEFITS IN MILLIONS)

Evaluation Year	Additional ADEs Avoided	Societal Benefit of Avoided ADEs
1	38	$7.0
2	627	$113.7
3	4,314	$781.9
4	16,845	$3,053.5
5	39,462	$7,153.4
6	60,634	$10,991.1
7	68,646	$12,443.6
8	64,486	$11,689.5
9	54,144	$9,814.7
10	41,344	$7,494.5
11	28,493	$5,164.9
12	17,523	$3,176.5
13	9,510	$1,724.0
14	4,531	$821.4
15	1,882	$341.1
16	678	$123.0
17	218	$39.4
18	51	$9.3
19	13	$2.3
20	0	0

K. 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 nonhospital 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 592 hours of pharmacist resources and 4,233 hours of nursing resources each year. The estimated annual efficiency savings of avoiding these opportunity costs equals $167,000. 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. If so, the total estimated annual efficiency gains to an average hospital would range from $209,000 to $334,000 from use of bar code scanners in pharmacies and patient care wards. These new operation efficiencies would continue beyond the evaluation period. If such gains were obtainable, the PV of these gains for the sector as a whole would be between $4.8 billion and $7.6 billion. The average annualized gains of these potential efficiencies are between $451.5 million and $721.5 million.

The proposed rule could also increase the use of medical informatics in locations other than hospitals. Other health care facilities, such as physician offices 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. We could not quantify the value of all of these expected additional uses of bar coding, but note that they are realistic and practical future uses of the technology.

L. 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 (JVR, 2002), 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 involved pregnancies with the remainder including surgical claims, misdiagnosis, and medication errors. If these claims are distributed equally by type and sector (inpatient and outpatient), we estimate that approximately 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 372,400). The average jury award for damages from medication errors was $636,800 in 2000, although only 40 percent of the cases were decided for plaintiffs. Estimated pre-trial settlements for malpractice claims in 2000 averaged $318,400. We do not have data on the proportion of settlements, but have assumed that 80 percent of claims are settled before trial. If so, the average likely award per preventable ADE is $532. Bar code systems are expected to avoid 12.8 ADEs per year in an average hospital. This implies an average reduction in annual legal awards of $6,800 per hospital and $43.9 million for all hospitals. Fewer awards would also result in lower malpractice insurance premiums, which would reduce other hospital expenditures. The General Accounting Office (GAO, 1995) 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 approximately $1,250 to $18,800 per bed. Although we were unable to quantify average hospital malpractice premiums or precise reductions in hospital liability insurance premiums due to the use of bar codes, the potential exists for industry savings. 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 (Lee et al., 1992) 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 approximately $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.

Although reduced lawsuits and liability insurance and increased cost capture represent transfers, they are also critical in determining whether and at what rate hospitals will adopt bar code technology. Combined with the efficiency gains explained previously, these transfers should allow hospitals to cover a significant portion of their bar code technology investment.

M. Comparison of Costs, Expenditures, and Benefits

The annualized costs of the proposed rule to the manufacturing, packaging, and labeling sectors totals $3.2 million. Hospitals would incur an annualized cost of $0.6 million to continue current operating practices. FDA resource costs to support the regulation equal an estimated $1.3 million per year. Thus, we estimate the annualized regulatory cost of the proposed rule to be $5.1 million. In addition, we expect the proposed 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 $680.0 million for the entire industry. Table 6 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. The estimated reduction in hospital operating expenses results from the assumption that hospitals could eliminate in-house labeling operations.

TABLE 6.—COSTS AND OTHER EXPECTED EXPENDITURES OF PROPOSED RULE (IN MILLIONS OF DOLLARS; 20-YEAR EVALUATION PERIOD; 7-PERCENT DISCOUNT RATE)

Industry Sector	Present Value of Costs	Annual Operating Costs at End of Period	Annualized Costs
Prescription Drugs	$30.4	$0.4	$2.9
OTC Drugs	$2.1	[1]	$0.2
Blood Products	$0.7	[1]	$0.1
Sub-Total Manufacturers	$33.2	$0.5	$3.2
Hospital Regulatory	$6.1	(-$0.7)[2]	$0.6
Sub-Total Private Sector Regulatory Costs	$39.8	(-$0.2)	$3.8
FDA Oversight	$13.8	$1.3	$1.3
Total Regulatory Costs	$53.1	$1.1	$5.1
Expected Expenditures From Healthcare Sector	$7,204.3	(-$348.8)[2]	$680.0

[1] Less than $0.05 million
[2] 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 $3.9 billion. This estimate includes the societal value of the avoided ADEs as well as the reduced hospital stays expected due to the earlier use of bar code reading technology. Other indirect potential benefits, such as efficient inventory control, patient tracking, electronic generation of daily reconciliation and medication reports, or other administrative gains were estimated to contribute an annualized amount of between $451.5 and $721.5 million in efficiency gains to hospitals. The likely distributional effects of revenue enhancement, other cost capture measures, or reduced legal costs are not completely quantified, but are likely.

If all costs and expenditures are combined, the annualized outlays total $685.1 million. The expected annualized public health benefit of over $3.9 billion far outweighs these outlays. Thus, the annual net benefits for the entire evaluation period are greater than $3.2 billion. Moreover, this calculation does not account for the potential efficiency gains as described above.

N. Uncertainty and Sensitivity

We recognize that the expected impacts of the proposed rule are based on a large number of uncertain assumptions. We attempted to account for this uncertainty by examining the key assumptions in the analysis.

1. Voluntary Share of Labeling Costs

The costs attributable to the proposed 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 30 percent of the required labeling costs would be attributable to the regulation, 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 regulation 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, 75 percent were attributable to the regulation, or all re-labeling costs were attributable to the regulation. These scenarios altered the current estimate of $3.2 million in annualized costs for manufacturers, repackers, and relabelers to a range of from $2.7 million (if all costs are considered voluntary) to $4.2 million (if no additional labeling costs are considered voluntary).

2. Packaging Decisions

We are sensitive to industry packaging decisions and asked our contractor to specifically assess the impact of the proposal 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 proposed rule would not have a significant impact on product packaging choices.

3. Mortality Associated with ADEs

FDA's contractor estimated that 2.8 percent of preventable ADEs 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: one percent and 0.1 percent. These rates reduce the expected value of an avoided ADE from $183,900 to $91,500 and $46,400, respectively, by changing the probability distribution of the expected outcomes of ADEs. The impact on the expected annualized benefits of ADE avoidance fall from $3.9 billion to $2.0 billion and $1.0 billion respectively. These estimated benefits continue to exceed the costs.

4. Value per QALY

There is no precise measure of value for quality-adjusted life-year. We have used 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 typical characteristics of the population for most of the wage premium studies) was adjusted for expected future bed and nonbed 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) may suggest a societal willingness-to-pay for a QALY. Cost-

effectiveness studies in the health economics literature have often relied on lower values, such as $100,000, to represent the monetary value of a QALY. In addition, the $5 million VSL is based on research conducted in the early 1990's and relies on relative risk and relative wages. Other typical estimates of the VSL have ranged from as low as $2 million to as high as $8 million.

We analyzed the societal benefit of the proposed rule using $100,000 as the QALY value for preventing a nonfatal ADE and the low VSL estimate of $2 million as the willingness-to-pay to avoid a fatality. The willingness-to-pay to avoid an average ADE decreased from $183,900 to $70,800 using these parameters. Overall, the estimated annualized benefit of the proposed rule fell from $3.9 billion to $1.5 billion, which would still exceed the estimated annualized costs.

5. 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 proposed rule. However, because we are not requiring hospitals to make this investment, we examined the impact of different diffusion rates. ERG examined two additional scenarios: one in which the technology is accepted within 20 years with a rule as compared to 30 years without a rule, and one in which technology is accepted within 15 years, as compared to 20 years with a rule. Both cases decrease costs and benefits. The first case reduced expected net annualized net benefits from $3.2 billion to $2.0 billion. Annualized hospital expenditures declined from $680 million to $408 million, and benefits decreased from $3.9 billion to $1.8 billion. The second case reduced annualized net benefits to $1.5 billion. Annualized hospital expenditures declined from $680 million to $303 million, and benefits decreased from $3.9 billion to $1.8 billion. The public health benefits of the proposed rule would still exceed costs and expenditures with these slower diffusion rates.

6. Hospital Intercept Rates with Machine-Readable Technology

The expected benefit of avoidance of patient ADEs is dependent 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 nonoptimal 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 660,400 and 165,000. The monetized annualized value of these avoided ADEs would vary from the current estimate of $3.9 billion to the lower and higher values of $1.6 billion (with a 20 percent improvement in interception rates) or $6.2 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.

7. 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. 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 $680.0 million to $246.7 million. However, if the productivity loss of nursing resources was 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. We recognize the extreme uncertainty of this projection and particularly invite public comment in this area.

8. Minimum Hospital Response

The expected benefits rely on a faster rate of hospital acceptance of bar code technology than the rate expected in the absence of a rule. The current estimate of public health benefits is based on all hospitals acquiring bar code systems within 10 years as compared to 20 years without the proposed rule. However, because we are not requiring hospitals to make this investment, we examined the minimum number of hospitals needed to install systems in order to be confident that benefits exceed costs. The ratio of costs to benefits implies that if only 0.05 percent of all hospitals in the United States (three facilities) make this investment 10 years earlier, the rule would generate sufficient public health benefits to justify costs. This estimate is based on average hospital size. We tested this assumption by assuming that only very small (fewer than 50 bed capacity) hospitals would adopt the technology. In this case, 22 hospitals would be required to adopt the technology (0.3 percent of all hospitals and 1.9 percent of all small capacity hospitals) in order for the expected benefits to exceed the costs.

9. 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 1,117 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 proposed 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 approximately $57,100. 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 1.7 avoided ADEs per year per facility. The estimated societal benefit of avoiding 1.7 ADEs is $303,800. If these small hospitals adopt technology at the same accelerated rate as all hospitals, the annualized benefit per hospital is $86,900, 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 $3,837 (1.7 ADEs avoided x $2,257) and annualized costs

of $57,100. 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 to 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.

O. Small Business Analysis and Discussion of Alternatives

We believe the proposed rule is unlikely have a significant impact on a substantial number of small entities. Despite this, we have prepared an initial Regulatory Flexibility Analysis (IRFA) and invite comment from affected entities. In addition, the regulation 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 proposal would directly affect manufacturers of pharmaceutical and biological products (NAICS 325412 and NAICS 325414), packaging services (NAICS 561910), and blood and organ banks (NAICS 621991), and indirectly affect hospitals (NAICS 622). We accessed data on these industries from the 1997 Economic Censuses and estimated revenues per establishment. Although other economic measures, such as profitability, may be preferable alternatives to revenues in 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 under 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 use standardized bar code information on their products. We estimate the annualized compliance costs for small entities in this industry at $600 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.

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 cost 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 with less that $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 would be required to apply standardized bar coded information on all blood products. This would require printing and process improvements to blood handling operations. We estimated the annual compliance cost for small entities in this industry at $100 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.

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 proposed rule. We anticipate that the rule would make the investment in bar code technology more attractive to hospitals, but the rule would not require such investments. Hospitals that have already installed bar code reading systems and internally affix self-generated information might need 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 proposed rule is estimated at $3,300 per facility, which is equal to less than 0.1 percent of 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 proposed rule. Each is discussed below. We invite comments and suggestions for additional potential alternatives.

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 proposal. 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 potential public health benefits for this additional information, and the estimated additional annualized cost of this

alternative was $46.0 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 currently rejected (although we invite comments on the OTC drugs to be covered) because the additional costs do not appear to be justified by the expected benefits. At this time, most noninstitutional 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 $1.9 million. The expected annualized costs of the regulation therefore would increase from $5.1 million to $7.0 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.

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 proposal would be much greater than the selected alternative. Annualized costs to manufacturers would increase to $8.3 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 $14.4 million. Consequently, we rejected the alternative of identifying a specific symbology.

3. Outreach

We held 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.

P. Conclusion

We have examined the proposed rule and find that the expected benefits outweigh the costs and that the regulation would improve public health. The detailed analysis that provides references and support for the summary that appears in this section is available in the docket as Ref. 46.

VIII. Request for Comments

In addition to requesting general comments on the proposal, and the specific requests on assumptions contained in the economic analysis, we are seeking comment on the following specific issues identified in the description of the proposed rule (presented here for the convenience of the reader):

1. Whether we should require bar codes on prescription drug samples, and the costs and benefits associated with such bar codes (see section II.B.2.a of this document).

2. The risks and benefits of including vaccines in a bar code rule (see section II.B.2.a of this document).

3. What terms we should use to describe OTC drugs that should be subject to the bar code requirement (see section II.B.2.b of this document).

4. Information on the costs and benefits associated with putting lot number and expiration date information in the bar code (see section II.C.2 of this document).

5. Whether the rule should refer instead to linear bar codes without mentioning any particular standard or refer to UCC/EAN and HIBCC standards (see section II.D.1 of this document).

6. Additional information regarding bar code scanning technology and the ability of bar code scanners to read different symbologies (see section II.D.1 of this document).

7. Whether the rule should adopt a different format (whether that format is a symbology, standard, or other technology), considering the following issues:

- What other symbol, standard, or technology should we consider, either in place of a linear bar code or in addition to it?
- How accepted is that symbol, standard, or technology among firms that would have to affix or use that symbol, standard, or technology?
- Will hospitals be able to read or use the symbol, standard, or technology, either with existing equipment or equipment under development? (see section II.D.1 of this document).

8. Whether any specific product or class of products should be exempt from a bar code requirement and the reasons why an exemption is considered to be necessary (see section II.F of this document). In addition, how could we create a waiver provision that would minimize the potential for misusing the waiver?

9. Whether the implementation period for a final rule can and should be shortened from 3 years to some other specific time period (see section II.G of this document).

10. Whether we should require the use of ISBT 128 for blood products, a specific symbology that is consistent with that required for drugs in proposed § 201.25, or ''machine-readable symbols'' as approved by the Director of CBER (see section II.H of this document).

11. How the proposed rule might affect hospitals where patients receive blood or blood components, particularly with respect to a hospital's decision to purchase a machine reader (e.g., scanner) that can properly identify the intended recipient of the blood or blood component, the machine readable information encoded on the blood or blood component label, and perhaps the linear bar codes appearing on drugs and OTC drugs that are dispensed pursuant to an order and commonly used in the hospital (see section II.H of this document).

12. Whether any of the alternatives discussed in the economic analysis have merit (see section VII.O of this document).

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments to http://www.fda.gov/dockets/ecomments or two hard copies of any mailed comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IX. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 am. and 4 p.m., Monday through Friday.

1. Institute of Medicine, ''To Err Is Human: Building a Safer Health System,'' 1999.
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27. Quality Interagency Coordination Task Force, ''Doing What Counts for Patient Safety: Federal Actions to Reduce Medical Errors and Their Impact—Report of the Quality Interagency Coordination Task Force (QuIC) to the President,'' at page 74 (February 2000).
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Appendix

Additional Information on Various Studies Identifying Different Types of Medication Errors

This appendix includes summaries of several articles that identify different types of medication errors, a table illustrating varied medication error rates among studies, and a list of references cited in the appendix.

I. Types of Medication Errors

Administering the Wrong Dose

Folli et al. examined errant chart orders in two large pediatric hospitals (Ref. A–1). The study defined an errant chart order as a potentially lethal error if certain consequences (such as cardiopulmonary arrest if administered at the dose ordered) resulted. The authors found that incorrect doses and missed doses were the most prevalent errors. Overdoses accounted for 55 percent of the dosing errors, while underdoses led to 26.9 percent of all errors.

In a study of adverse events in hospitalized patients, Leape et al. reviewed 30,195 randomly selected hospital records and identified 1,133 patients whose disabling injuries were caused by medical treatment (Ref. A–2). Errors in dose or method of use accounted for 42 percent of all errors.

In a study of two urban teaching hospitals, Kaushal et al. found dosing errors to be the most frequent medication error (which the authors defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring) and the most frequent preventable adverse drug event (Ref. A–3).

Lesar et al. conducted a study of prescribing errors at a teaching hospital (Ref. A–4). The authors' review of 289,411 medication orders revealed 905 prescribing errors that were detected and averted, and overdoses and underdoses accounted for 28.7 and 17.8 percent of total errors respectively.

McCarthy, Kelly, and Reed studied the medication administration practices of school nurses (Ref. A–5). The authors found that 48.5 percent of school nurses surveyed reported medication errors, and overdoses or double doses were the third most commonly reported error (22.9 percent of medication errors).

Administering a Drug to a Patient Who Is Known to Be Allergic

In the Lesar review of medication orders, 6.7 percent of all medication order errors that were detected and averted involved prescribing a drug to a patient who is allergic to the prescribed drug (Ref. A–4).

In an article by Classen et al. involving a case control study of all patients admitted to a hospital in a 3-year period, medication errors due to known drug allergies represented 1.5 percent of all adverse drug events, and all were preventable (Ref. A–6).

Administering the Wrong Drug to a Patient or Administering a Drug to the Wrong Patient

A study by Thur et al. observed how nurses in two surgical units prepared to administer parenteral admixtures (which the authors defined as including only fluids to which one or more drugs were added directly into a single or primary bottle) (Ref. A–7). The authors defined ''medication error'' as including the administration of the wrong drug or solution, the wrong dosage of a drug or solution volume, an unordered or discontinued drug, or two or more pharmaceutically incompatible drugs in the same admixture. The study involved 100 observations where 331 parenteral admixtures were prepared; unordered drugs accounted for 3 percent of the errors that were observed. In one instance, the drug was administered two times per day for 4 days, even though the order for the drug had been discontinued earlier.

In the Classen et al. article that involved a case control study, of 905 prescribing errors that were detected and averted, 1.1 percent of all errors involved prescribing a drug to the wrong patient (Ref. A–6).

Administering the Drug Incorrectly

In the study by Kaushal et al. that examined 10,778 medication orders at two urban teaching hospitals, errors involving the drug's route of administration were the second most common form of medication error and accounted for 18 percent of the medication errors (Ref. A–3). These medication errors also accounted for the third-most common form (14 percent) of potential adverse drug events, which the authors defined as a medication error having a significant potential for injuring a patient.

Administering the Drug at the Wrong Time or Missing Doses

In a study of two pediatric critical care units by Tisdale, ''wrong time'' errors, which were defined as medications administered 30 minutes before or after the scheduled administration time, were the most prevalent error and accounted for a 16 percent error rate (Ref. A–8).

In McCarthy, Kelly, and Reed's study of school nurses, of the 315 school nurses who reported a medication error, 251 cited missed doses as the most common medication error (Ref. A–5).

In their study of the relationship between medication errors and adverse drug events, Bates, Boyle, et al. found that 53 percent of the medication errors surveyed involved at least one missing dose of medication (Ref. A–9).

A recently published study by Barker et al. examined 36 institutions in Colorado and Georgia and found that 19 percent of the doses administered were in error and that the most prevalent error (at 8 percent of the medication errors) was ''wrong time'' medication errors (Ref. A–10). The authors defined ''wrong time'' as administration of a dose more than 60 minutes before or after the scheduled administration time, or a 30 minute window for medications that were ordered before, with, or after a meal. However, the ''wrong time'' medication error rate ranged between zero percent for some nonaccredited hospitals in Georgia to 26.2 percent for a nonaccredited hospital in Colorado.

II. Frequency of Medication Errors

Table 1 illustrates the variation in medication error rates among several studies. Some studies suggest a medication error rate of under 7 percent, whereas others suggest a rate at or above 20 percent. The differences may be due, in part, to different definitions of medication error or different research methodology that focused on fatalities, injuries, or medication orders.

TABLE 1.—MEDICATION ERROR RATES REPORTED IN VARIOUS STUDIES

Study	Definition of Medication Error Used	Medication Error Rate
Observation of nurses in two surgical units by Thur (Ref. A–7).	''Medication error'' defined as wrong drug or solution; wrong dosage of a drug or solution volume; an unordered or discontinued drug; or two or more pharmaceutically incompatible drugs in the same admixture.	21%.

TABLE 1.—MEDICATION ERROR RATES REPORTED IN VARIOUS STUDIES—Continued

Study	Definition of Medication Error Used	Medication Error Rate
Review of 101,022 medication orders at 2 pediatric hospitals by Folli et al. (Ref. A–1).	''Errant medication order'' considered to be an order that was not in accordance with standard pediatric references, current published literature, or dosing guidelines approved by the hospital's pharmacy and therapeutics committees.	Medication order error rate was between 4.9 and 4.5 errors per 1,000 orders.
Review of 289,411 medication orders written during a 1-year period by Lesar (Ref. A–4).	Not defined.	Prescribing errors were detected at a rate of 3.13 errors per 1,000 orders.
Survey of 26,462 patients in 7 countries; 24 were considered to have died as a result of a drug or group of drugs, by Porter and Jick (Ref. A–11).	''Suspected adverse reactions'' defined as any undesired or unintended effect of a drug.	0.02% fatality rate (6 deaths were considered preventable).

TABLE 1.—MEDICATION ERROR RATES REPORTED IN VARIOUS STUDIES—Continued

Study	Definition of Medication Error Used	Medication Error Rate
Review of 30,195 randomly selected hospital records by Leape et al. (Ref. A–2).	''Adverse event'' defined as an unintended injury caused by medical management and resulted in measurable disability. The reviewers considered an adverse event to be due to ''negligence'' if they felt there was a deviation from accepted norms of treatment and after they considered other factors (such as potential consequences, frequency of risk, degree of emergency, and complexity of the case). The authors defined ''negligence'' as failure to meet the standard of care reasonably expected of an average physician qualified to take care of the patient in question.	Of the adverse events due to drug treatment, 18% resulted from negligence, although the authors also explain that negligence occurs not merely when there is error, but when the degree of error exceeds an accepted norm.

TABLE 1.—MEDICATION ERROR RATES REPORTED IN VARIOUS STUDIES—Continued

Study	Definition of Medication Error Used	Medication Error Rate
Study of 18,262 medication and intravenous fluid orders given in a 3–month period at a children's hospital by West et al. (Ref. A–12).	Not defined.	Medication order error rate ranged between 2.6 to 8.5 per 1,000 orders. Verbal medication orders had the lowest error rate, followed by computer-entered orders (6.3 per 1,000) and handwritten orders.
Study of 4,031 adult admissions of 11 medical and surgical units in 2 hospitals by Bates, Cullen et al. (Ref. A–13).	''Adverse drug event'' defined as an injury resulting from medical intervention related to a drug.	28% of adverse drug events are preventable, and there were 7.3 preventable adverse drug events per every 100 admissions.
Review of 10,070 medication orders to identify medication errors by Bates, Boyle et al. (Ref. A–9).	''Medication error'' defined as errors in the process of ordering or delivering medication, regardless of whether an injury occurred or the potential for injury was present.	5.3%.

TABLE 1.—MEDICATION ERROR RATES REPORTED IN VARIOUS STUDIES—Continued

Study	Definition of Medication Error Used	Medication Error Rate
Matched case-control study of all patients admitted to a hospital in a 3-year period by Classen et al. (Ref. A–6).	''Adverse drug event'' defined as an event that is ''noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis, therapy, or modification of physiologic functions'' but excludes therapeutic failures, poisonings, and intentional overdoses.	1% of all adverse drug events, but the authors also state that almost 50% of all adverse drug events are potentially preventable.
Review of 10,778 medication orders at 2 urban teaching hospitals by Kaushal et al. (Ref. A–3).	''Medication errors'' defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring.	5.7%, with adult patients cared for in a pediatric setting experiencing the most medication errors.
Prospective cohort study in 36 institutions by Barker et al. (Ref. A–10).	''Medication error'' defined as a dose administered differently than as ordered on the patient's medical records.	19%, or nearly 2 errors every day for a typical patient receiving 10 doses per day, or, for a facility with 300 patients, almost 40 potential adverse drug events in a facility. The percentage of potentially harmful errors was 7% or more than 40 per day per 300 inpatients.
Examination of all U.S. death certificates between 1983 and 1993 by Phillips et al. (Ref. A–14).	''Medication errors are ''accidental poisonings by drugs, medicaments, and biologicals'' and have resulted from ''acknowledged errors, by patients or medical personnel.	Medication error rate rose from 1 out of every 439 outpatient deaths and 1 out of every 1, 622 inpatient deaths in 1983 to 1 out of every 131 outpatient deaths and 1 out of every 854 inpatient deaths in 1993. The authors suggest the increase may be due to an increasing willingness to attribute error deaths that were previously ascribed to natural causes.

III. References in the Appendix

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 am. and 4 p.m., Monday through Friday.

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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, it is proposed that parts 201, 606, and 610 be 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 OTC drug product that is regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act are subject to the bar code requirements in this section unless they are exempt from the registration and drug listing requirements in section 510 of the act.

(b) What drugs are subject to these bar code requirements? The following drug products are subject to the bar code label requirements: Prescription drug products (excluding samples), biological products, and over-the-counter drug products that are dispensed under an order and are commonly used in hospitals. For purposes of this section, an over-the-counter drug product is ''commonly used in hospitals'' if it is packaged for institutional use, labeled for institutional use, or marketed, promoted, or sold to hospitals.

(c) What does the bar code look like, and where does the bar code go?

(1) Each drug product described in paragraph (b) in 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 Uniform Code Council (UCC/EAN) 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 act.

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 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, repackage, 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.

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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.

Unless it is regulated as a device, a biological product must comply with the bar code requirements at § 201.25 of this chapter.

Dated: January 24, 2003.

Mark B. McClellan,

Commissioner of Food and Drugs.

Dated: February 6, 2003.

Tommy G. Thompson,

Secretary of Health and Human Services.

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