

***Draft Final***  
***Economic Impact Analysis***  
*For A Prospective FDA Rule Governing:*

**Foreign and Domestic Establishment Registration and Listing  
Requirements for Human Drugs,  
Certain Biological Drugs, and Animal Drugs**

Submitted to:

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## **EXECUTIVE SUMMARY**

Based on FDA's interest in improving the precision of current drug identification systems, the Agency is proposing revisions to existing establishment registration and drug listing rules, including the following:

- New methods for assigning NDC numbers
- When and how to register and list drugs
- The information to be provided for each registration/listing
- Requirements for electronic submission of registration and most listing data
- Requirements to print National Drug Code (NDC) numbers on all drug labels (NDCs are not currently required on labels for all drugs)

The proposed rule will modify the NDC assignment system in that FDA will assign the 3 segments (the labeler, product, and package code) of the NDC number. Currently, manufacturers and other labelers each receive a "labeler" code from FDA and they are then free to assign

product and package codes according to any process they care to apply. With the proposed rule, FDA will continue to assign new labeler codes using current practices and assign the product and package codes. For a new strength of an existing drug product, FDA will assign a new product code using a consistent process instead of the manufacturer assigning the new product code.<sup>1</sup> For a new package of an existing product, FDA will assign a new package code using a consistent process.

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<sup>1</sup> This report uses the term product or drug product to mean an active pharmaceutical ingredient (API), finished drug product, or biologic that is subject to the proposed rule.

ERG contacted pharmaceutical manufacturers, drug distributors, pharmacists, pharmacy benefit managers (PBMs), and developers of industry software about the prospective changes. ERG determined that one major impact of the proposed rule is the cost associated with the loss of existing numerical patterns in product codes, due to the use of centralized, consistent process for assigning product codes.<sup>2</sup> Other potential costs to healthcare entities include time lags due to FDA assignment of NDC numbers (e.g., slower turnaround of NDC numbers by FDA, having to change data submitted with NDC number due to changes in product formulation, etc.), and other minor changes. While many respondents had impressions of how the changes might affect their business, very few could give specific estimates of the implications for their businesses. Thus, the estimates below describe only approximate impacts and reflect a large degree of uncertainty.

Other impacts of the proposed rule are the costs to update package labels to comply with a requirement to have all NDC numbers include the prefix “NDC,” costs to submit content of labeling electronically for many products not already subject to this requirement, and costs to set up a system (acquiring software and training staff) for the electronic submission of NDC information, content of labeling, product listings and changes, and establishment registrations.

For the change in assigning the product code and package code using a centralized, consistent process leading to the potential for losses of “intelligence”, ERG forecast an estimated first-year cost of \$3.8 million and a recurring annual cost of \$3.2 million. If FDA requires all labeler codes to be consolidated at the parent company level (currently not assumed to be the case), additional manufacturer costs will be incurred.

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<sup>2</sup> For example, currently a manufacturer might assign the same first two or three digits (e.g, 004) to the same product, with the last digit varying to designate a different strength of the product. Often these are assigned sequentially as well (e.g., product code for 100 mg. strength is 0046, for 250 mg. is 0047, and for 500 mg. is 0048).

Costs for updating package labels will be somewhat mitigated because the long implementation period for the regulation will allow many labels to be changed in the course of the relatively frequent label changes in the industry. However, some pharmaceutical manufacturers will still need to revise their labels in response to regulatory requirements. This and other minor provisions that might require product labeling to be revised will generate first-year costs of approximately \$35.4 million. Costs to submit content of labeling, a new requirement for most OTC products, are estimated to be \$1.7 million annually. Costs to obtain software and train employees for electronic submission of materials to FDA are expected to be \$1.4 million in the first year.

Costs for obtaining NDC numbers for new products each year, costs for electronically submitting registration and listing information, including changes, and costs for newly covered entities to undertake the NDC application and registration and listing process will generally be offset by the cost savings represented by time saved by industry when using the electronic submittal processes (Appendix A presents the comparison of costs and costs saved). Combining and annualizing all costs considered not to be offset by cost savings generates a total annualized cost of \$10.7 million over 10 years and at a 7 percent discount rate (Appendix B also discusses how total annualized costs are affected by changes in the currently proposed implementation periods for the NDC number requirements of the rule).

As a regulatory alternative, ERG also investigated complete randomization of the NDC number for new products, with all other provisions of the rule unchanged. In this case, FDA would assign a random, 10-digit, unique NDC number for new products. This alternative shows the potential to require much higher compliance costs for industry, e.g., \$916 million in first-year costs.

## **SECTION ONE**

### **THE EXISTING SYSTEM FOR DISTRIBUTING NDC NUMBERS**

The NDC number was introduced over twenty years ago as a means of identifying individual drug packages, by distinguishing specific dosage strengths and package sizes. With its history of industry use, the number of ways in which the NDC number is used among healthcare companies is widely varied. At a minimum, the insurance industry infrastructure is heavily dependent upon NDC numbers to track drug expenditures (Bizzaro, 2002).

Compendium service companies, such as First DataBank, Multum Information Services, and Medi-Span, assemble and distribute information to entities that use NDC and related drug product information for their operations. The compendium companies serve as central repositories for NDC and Universal Product Code (UPC) numbers. Manufacturers distribute new product identification data (i.e., NDC numbers) to the compendium companies and compendium companies then provide product listing updates more or less frequently to their clients, depending upon their contractual agreements. The compendium company clients include retail stores, hospitals, PBMs, pharmaceutical manufacturers, insurance firms, electronic medical record companies, and others. Compendium companies distribute drug information to clients who then incorporate it into their software to facilitate scanning (such as by cashiers) or the operation of their data processing systems. In addition to the NDCs, some compendium company databases cover drug product identification, drug description, and drug price information. Much of the demand for compendium data derives from the inclusion of pricing data.

The NDC number consists of 10 digits, including a 4 or 5 digit labeler code, a 4 or 3 digit product code, and a 1 or 2 digit package code. The components are presented in one of three

formats, 4-4-2, 5-3-2, or 5-4-1. While most NDC numbers in their original state consist of 10 digits (and are so presented on product labels), the compendium companies convert the NDC number to 11 digits in a 5-4-2 format (i.e. 5 digit labeler code, 4 digit product code, and 2 digit package code) for use in industry databases. To convert the NDC numbers, the compendium companies follow a renumbering protocol developed by the National Council for Prescription Drug Programs (NCPDP). A leading zero is added where the original NDC structure deviates from the 11 digit structure of 5-4-2, as follows:

- With a 4-4-2 NDC, a leading zero is added to the beginning of the labeler code
- With a 5-3-2 NDC, a leading zero is added to the beginning of the product code
- With a 5-4-1 NDC, a leading zero is added to the beginning of the package code

Drug identification and price data must be frequently updated. Generic relabeling companies and OTC manufacturers modify their product lists so quickly that substantial updating of the databases is needed. One account executive estimated that his firm deals with 60,000 to 80,000 changes in drug information per year (Mussato, 2003). This routine turmoil in the drug marketplace poses a challenge for the compendium companies to maintain an entirely accurate repository of NDC numbers. Despite the existence of the compendia, many users of NDC and bar code information, such as the Veterans Administration Centralized Mail Order Pharmacies, encounter numerous problems interpreting the product labeling they receive (Pierce, 2001).

## **SECTION TWO**

### **ASSIGNMENT AND PRESENTATION OF NDC NUMBERS**

As noted in Section One, the NDC number consists of 3 components (i.e., the labeler, product, and package code). FDA currently assigns the labeler code of the NDC number. Firms (including bulk, OTC, and prescription drug product manufacturers, and possibly repackagers, relabelers, and private label distributors if they use their own NDC numbers on their labels) currently determine the product and package codes of the NDC number for their products.<sup>3</sup> The assignment of each of these components is discussed in further detail below, followed by a discussion on the presentation of NDC numbers on packaging by bulk pharmaceutical manufacturers (also known as active pharmaceutical ingredient (API) manufacturers),

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<sup>3</sup> Drug salvagers, although they would be required by the proposal to list, are not required to obtain an NDC, nor can they use an NDC other than what was on the original packaging if the finished or bulk product is returned to commercial distribution. Salvagers are generally the original manufacturers of the finished or bulk product (Cooley, 2005). ERG was unable to find any examples of independent drug salvagers.

prescription and OTC drug product manufacturers, biologics license holders, repackagers and relabelers, and, in some instances, private label distributors.<sup>4</sup>

## **2.1 Assignment of NDC Numbers**

**Labeler Code.** While FDA currently assigns only one labeler code to each manufacturer, relabeler, repackager, or private label distributor, the large number of mergers in the manufacturing industry has resulted in many of the consolidated manufacturing companies owning multiple labeler codes. Manufacturers often continue to use all of the labeler codes of the companies they have acquired in order to avoid changing the NDC number for existing products. FDA would require each new product, either a finished or bulk drug product or biologic (drug product or product is used in this report to reflect all types of products) brought into commercial distribution by a firm with several labeler codes assigned to it, to be assigned only one of the multiple labeler codes from the effective date of the regulation onward. While not a requirement, some manufacturers might slowly migrate to one labeler code as they take their products off the market (Baxter, 2004). Others might close out old labeler codes when mergers occur (McTiernan, 2004). Currently, some manufacturers use labeler codes to distinguish between different divisions of a company (e.g., Novartis Consumer Health, Novartis Ophthalmic, and Novartis Consumer Health). ERG assumes that labelers will not be required to consolidate

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<sup>4</sup> APIs would only be covered by the proposal if they enter commercial distribution, that is, a bulk drug shipped from one site to another site owned by the same firm would not be assigned an NDC number; this product would be exempt from all requirements under the proposal, including listing.

labeler codes at the parent company level, but will be able to have divisions and subsidiaries continue to use their own labeler code as long as only one code per registrant is used subsequently.

**Product Code.** Pharmaceutical manufacturers and other NDC number holders have varied approaches to handling the product code section of the NDC number. Most assign their product codes in one of two ways:

- Sequentially, to facilitate data analysis and/or for purposes of systematically assigning product codes
- In predefined blocks of numbers assigned to each operating department

Numerous manufacturers use the product code to define product sequences, so that the different versions of a product (i.e., different strengths, flavors, or package types) have sequential product codes. While usually not assigned for this purpose, patterns in product code assignments can facilitate data analysis, such as where an analyst can sort database information by NDC numbers, including the product code sequence. Based on a cursory analysis of the 2003 Drug Topics Red Book, these patterns are much more prevalent in prescription than OTC drug products (Drug Topics Red Book, 2003). Some manufacturers assign product codes sequentially to new products, not to facilitate data analysis, but because it is easier to have a logical system in place to keep track of numbers that have been used (McTiernan, 2004).

Other manufacturers, however, do not coordinate NDC number assignment practices within their company. For example, a large manufacturer might allocate their available product codes in blocks to different operating departments. Thus, the product numbers 1000 through 1500 might be reserved for the heart medication department. Each department might then assign their product codes in an independent fashion (Cooley, 2002).

**Package Code.** Package codes are sometimes assigned based on the contents of the product (e.g., for a 30 tablet bottle, 30 might be used as the package size). Again, this is more often seen in the prescription than the OTC industry. An examination of NDC numbers listed in the Red Book, however, shows that even in the prescription industry, many package codes have no easily discernible meaning (Drug Topics Red Book, 2003).

## **2.2 Presentation of NDC Numbers**

**API Manufacturers.** Although some API manufacturers might print NDCs on product labels, most do not (Cooley, 2005). Furthermore, not all API products have labels per se. Large volume shipments, such as those sent by tank cars, use bills of lading to serve a similar purpose (Cooley, 2005). Including NDC numbers on bills of lading should not be problematic, since one would be prepared individually for each shipment.

**Prescription Manufacturers.** In the prescription industry, the NDC number facilitates the insurance system reimbursements covering drug purchase costs. Thus, NDC numbers on prescription products are usually presented in bar code format on exterior labels, with all 3 components listed (labeler, product, and package code). Exceptions exist, however. For example, manufacturers have difficulty printing the NDC number and/or barcoded NDC number on small drug labels and packages with extremely limited label surface area.

**OTC Manufacturers.** NDC numbers are not as widely used in the OTC manufacturing industry. Instead, OTC manufacturers consistently present UPC bar codes on their product labels, either in addition to or in lieu of NDC numbers. UPC numbers are one of several trade identification systems organized by the Uniform Code Council (UCC), an industry-sponsored

association created to develop multi-industry product identification systems (UCC, 2003a). The UPC code was designed to facilitate commercial transactions in the retail sector, including drug stores, mass merchandising locations (such as supermarkets and discount store chains), convenience stores, and other locations with OTC sales. Because the majority of OTC products are sold in the retail sector, all but a very small percentage of products show a UPC bar code. Given that prescription products are not normally scanned at retail drug store counters, UPC numbers generally are not relevant to prescription drugs.

While the very large majority of OTC products carry a UPC label, there are variations in the formatting and content of the UPC numbers. A substantial share of products present a UPC number and make no mention of an NDC number. The UCC website states that the presence of the prefix “3” indicates that the following number is either an NDC or an Health Related Items Code (HRIC) number (UCC, 2003b). In a large majority of cases, it is the NDC number (Bizzaro, 2002). This relationship can also be affirmed on those packages (a small minority) that print the NDC separately from the bar code on the package. Other products separately print the NDC number, however, and it is not the same as the UPC.



**Repackagers and Relabelers.** Among drug repackagers and relabelers, the very large majority provide NDC numbers in bar code formats on their products. In a few cases, however, firms do not provide an NDC number or provide only a partial one, thus creating some potential confusion in prescription drug reimbursement channels. According to one compendium representative, for example, repackagers occasionally reuse NDC numbers, either because they have run out of available numbers or because they have mistakenly selected an already active NDC number. Also, a repackager might present the first two sections (labeler code and product code) of the product they are handling, but leave off the final two digits, representing the package code (Meredith, 2003).

Further, some repackagers present the manufacturer NDC number instead of their own when repackaging larger products into smaller packaging for pharmacies. Medicaid uses the NDC number on the package to file rebate claims with a firm. Thus, it should be noted that there are likely to be potential impacts on repackagers if their NDC numbers are required on packages.<sup>5</sup>

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<sup>5</sup> Rebates are paid by manufacturers when repackaged products present the manufacturer NDC number on the packaging. A requirement to present the repackager's NDC number on the packaging would change this arrangement. Repackagers argued to ERG, however, that they are in no position to pay rebates to Medicaid. Their profit margins are 1 to 2 percent and would be more than completely eradicated by rebates (Giacaloni, 2004).



### **SECTION THREE**

#### **COST IMPACTS OF NDC NUMBERING SYSTEM CHANGES ON VARIOUS ENTITIES**

Under the proposed rule, FDA will take over assignment of the product and package codes of the NDC number. For a new strength of an existing product (either finished or bulk), a new product code would be assigned by the FDA instead of a new product code being assigned by the manufacturer. For a new package of an existing product, a new package code would be assigned. Existing numbers would not be affected. All existing features of the NDC number would be retained (i.e., 10 digits organized into 3 groups of codes). In terms of cost to the industry, these changes to the NDC numbering system might result in a significant cost. The other cost impacts are discussed in Section 4.

ERG solicited comments from chain drug stores, manufacturers, distributors, PBMs, pharmacists and pharmacy software providers, other healthcare data infrastructure companies, compendium companies, and hospital pharmacists. Under the assumption that FDA would assign product and package codes using a centralized, consistent process, the proposed change to the NDC numbering system could affect the “intelligence” of the product and package components of the NDC code, while leaving the labeler code unaffected. However, it is not clear how companies use “intelligence” in the product or package code because of the variety of ways the product and package codes are assigned. In addition, companies can change the method for assigning the product or package code without any warning. Because the “intelligence” of the product and package components is only used by certain groups in the industry, the impacts on the healthcare data processing infrastructure will be limited. The primary sources of economic impacts are pharmaceutical benefit management tasks, such as the generation and maintenance of drug formularies, as currently performed by a subset of companies, as well as data analysis done by manufacturers, especially with respect to rebates and market analysis/forecasting. Table

3-1 identifies many of the healthcare entities potentially affected by a change in the NDC number, including pharmaceutical manufacturers, drug wholesaler/distributors, pharmacies, state Medicaid agencies, and others. Relabelers, repackagers, and private label distributors are not included on this table. Relabelers and repackagers are not expected to be affected by the prospective FDA assignment of product and package codes, since they generally have not used their own NDCs on packaging in the past. Distributors that print their own NDC numbers on their labels are also considered relabelers. No discernible impact is seen for private label distributors who can no longer place their NDC numbers on their labels (Cooley, 2005). Table 3-2 summarizes the estimated impacts of this section.

Note that this table estimates 746 firms in the pharmaceutical industry as potentially affected by this loss of “intelligence”. The count is based on 666 firms identified in the Orange Book, and an estimated 80 firms producing animal drugs (Census Bureau, 2004). These latter might not produce animal drugs exclusively so there might be some overlap in these counts. The much larger count of domestic pharmaceutical firms in FDA’s registration database (5,441 firms; Smith, 2003) is the result of duplicative counts of potentially numerous levels of corporate structure (direct owners of sites, owners of these firms, other intermediary firms, merged entities no longer in legal existence, corporate parents, various corporate divisions that are not distinct corporate entities, and other variations). ERG assumes that the impact of the loss of intelligence is measurable at the top level of the corporate entity (i.e., the highest level of ownership) and, therefore, uses the 746 estimate of the number of corporate entities.

### **3.1 Pharmaceutical Manufacturers**

Pharmaceutical manufacturer practices likely to be affected by the changes proposed in the rule include:

- Rebate processing work, including analysis of payment history and settlement of disputes
- Market research analysis

These are discussed in further detail below.

Under signed agreements, pharmaceutical manufacturers provide cash rebates to Medicaid, PBMs, or other types of insurers if the manufacturer's drugs are used by the insurer's enrollee. Manufacturer staff review rebate invoices, make corrections, and send out rebate payments to the insurers.

At some manufacturers, the relevant data processing work is partly dependent upon the components of the NDC number. For example, Eli Lilly employees described their process for verifying the state reimbursement data in an industry publication (Brown and Lewis, 1995). They group their reimbursement data files by product code and then assess the nature of the apparent disputes with state reimbursement amounts. (Many rebate disputes originate from information about the product or package characteristics.)

Other manufacturers contacted also described how they use the product code, and less frequently, the package code, to group products in order to analyze payment history and resolve disputes in Medicaid and other rebates (Baxter, 2004; Yadechevich, 2004). These groupings are usually done using spreadsheets in which manufacturers arrange products based on the numbering sequence found in product codes. They might also build “macro” programming, a built-in tool available in many software programs, on the ordering.

With FDA assignment of the product code and package code of NDC numbers, manufacturers might need more time to manually group products to derive the same information. Also, more data entry work might be needed. In some instances, companies might add a data

**Table 3-1 Count of Potentially Affected Healthcare Entities**

Type of Entity	Establishments	Source	Additional Comment
Pharmaceutical manufacturers (human)	666	Orange Book, 2003	Includes only those pharmaceutical firms that have at least one currently marketed product in the U.S. Might be an overestimate due to the possibility of applicant name duplication in the database. Does not include firms that only manufacture unapproved drug products.
Pharmaceutical Manufacturers (animal)	80	Census, 2004	Includes firms that own establishments that manufacture animal drugs. Includes some firms that manufacture both human and animal drugs, so overstates the number that manufacture animal drugs exclusively. Does not include firms that only manufacture unapproved drug products.
Pharmacies	67,434	NA	Sum of pharmacy categories (chain store headquarters offices are not counted in this total)
Chain store (headquarters office)	25	NWDA, 2000	Covers headquarters for firms ranging from CVS (4,100 stores) to companies operating over approximately 35 stores.
Chain	20,493	NACDS, 2001	National Association of Chain Drug Stores Web Site ( <a href="http://www.nacds.org">www.nacds.org</a> )
Independent	24,500	NCPA, 2002	National Community Pharmacists Association Web Site ( <a href="http://www.ncpanet.org">www.ncpanet.org</a> )
Mass merchant	5,910	NACDS, 2001	National Association of Chain Drug Stores Web Site ( <a href="http://www.nacds.org">www.nacds.org</a> )
Supermarket	8,531	NACDS, 2001	National Association of Chain Drug Stores Web Site ( <a href="http://www.nacds.org">www.nacds.org</a> )
Institutional	7,950	ERG, 2001	Profile of the Pharmaceutical Compounding Industry: Draft Final Report. Submitted to FDA, Office of Policy, Planning, and Legislation. Office of the Commissioner. August 27.
Mail order	50	ERG, 2001	Based on discussions with Winkelman (2004)
Pharmacy benefit management companies (PBMs)	76	ERG, 2001	Profile of the Prescription Drug Wholesaling Industry: Final Report. February 12. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The figure is reported by SMG Marketing Group, Inc.
Hospitals	6,116	AHA, 2002	American Hospital Association Web Site ( <a href="http://www.ahadata.org">www.ahadata.org</a> )
Compendium companies	5	ERG, 2004	Estimate based on discussions with Winkelman (2004)
Wholesalers/distri	6,500	ERG,	Profile of the Prescription Drug Wholesaling Industry:

butors		2001	Final Report. February 12. Submitted to Office of Policy, Planning, and Legislation, Office of the Commissioner, FDA. The report notes that this is probably an underestimate
Group purchasing organizations	701	ERG, 2001	See note immediately above.
State Medicare agencies	50	ERG, 2003	Allocated one per state.
Physician offices	195,655	Census, 2000	NAICS 62111 from County Business Patterns 2000, U.S. Census Bureau.
Dentist offices	116,494	Census, 2000	NAICS 62121 from County Business Patterns 2000, U.S. Census Bureau.

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

**Table 3-2. Proposed Rule - Costs of NDC Changes for Affected Health Sector Entities (a)**

Type of Entity	Establishments	Share of Estab. With Costs	Cost per Establishment		Aggregate Costs		Additional Comment
			First-Year	Recurring Annual Cost	First-Year	Recurring Annual Cost	
Pharmaceutical manufacturers	746	100%	\$5,120	\$1,600	\$3,819,520	\$1,193,600	A calculated cost for Medicaid rebate, market analysis, and other affected departments to map newly assigned NDC numbers to continue. All vendors are expected to be affected.
Pharmacies	67,434	N/A	Modest, not quantified	Modest, not quantified	Modest, not quantified	Modest, not quantified	Per pharmacy costs based on assumption that vendors modify software and provide to pharmacies free of charge with software updates. Some initial retraining or reorientation costs were not quantified.
Pharmacy chain store/for PBM-like tasks (headquarter offices)	25	10%	N/A	\$200,000	N/A	\$500,000	Costs based on discussion of additional labor for data entry with chain store information technology managers (Klimek, 2003). Costs of related procedural changes needed in 1st year were not quantified.
Pharmacy benefit managements (PBMs)	76	10%	N/A	\$200,000	N/A	\$1,520,000	Estimate parallels that for chain store pharmacy headquarters; a small share of entities will need to modify systems.
Hospitals	6,116	N/A	Modest, not quantified	Modest, not quantified	Modest, not quantified	Modest, not quantified	Assumed to be largely unaffected by the change in NDC numbers. Adjustments in pharmacies are possible, however, at the same rate as estimated for other pharmacies.
Compendium	5	N/A	Negligible	Negligible	Negligible	Negligible	No direct impacts forecasted.

companies							
Wholesalers/ distributors	6,500	N/A	Negligible	Negligible	Negligible	Negligible	Preservation of the labeler component of the NDC is judged sufficient to allow these IT systems to continue with virtually no affect.
Group purchasing organizations	701	N/A	Negligible	Negligible	Negligible	Negligible	Most automation systems assumed to accommodate change without modification.
State Medicaid agencies	50	N/A	Negligible	Negligible	Negligible	Negligible	Preservation of labeler code is judged to allow continuity of current reimbursement system.
Physician offices	195,655	N/A	Negligible	Negligible	Negligible	Negligible	No direct impacts forecasted.
Dentist offices	116,494	N/A	Negligible	Negligible	Negligible	Negligible	No direct impacts forecasted.
<b>Total</b>			<b>\$5,120</b>	<b>\$401,600</b>	<b>\$3,819,520</b>	<b>\$3,213,600</b>	

N/A—not available.

(a) Estimates prepared by ERG based on discussions with representatives of the groups shown or extrapolations based on estimated costs for similar organizations. ERG is responsible for all quantification of impacts as industry representatives could provide only qualitative information on the potential impacts. Estimates should be considered speculative. Estimates are considered to be net of cost savings for possible improvements in data processing under a centralized NDC number assignment system.

field to retain the ability to order products on the basis of a product code. None of the manufacturers contacted were able to quantify the exact impact of the NDC changes, however.

Market research departments also make use of the NDC number in similar ways when performing marketing and forecasting-related functions. These staff might wish to aggregate data on the basis of a given product strength or package size and therefore make use of the NDC components in electronic data sorting of NDC numbers. Sometimes the first few digits in a product code are used as a basis for sorting (Peterson, 2004).

A few manufacturers noted that FDA assignment of the product and package code, if random, could result in more errors due to the loss of familiarity with the number, especially at the pharmacy level. Many employees have memorized the blocks of numbers assigned to product groupings and the meaning of package codes. Loss of meaning to these numbers would make it harder to recognize a product by the NDC number and could thus increase errors and make them harder to catch.

Other than these functions, however, most pharmaceutical manufacturers stated that they made little use of the internal intelligence of the NDC numbers. Product codes are not always assigned in an orderly fashion for their database programs to use the information. Manufacturer database programs, therefore, generally only use the combined labeler, product, and package code information as pointers to a specific stock-keeping unit (SKU). This information is equivalent to a product strength/dosage form/package size designation and, therefore, is generally equivalent to an NDC number assignment.

The potential loss of ability to group products based on product code or package code might require staff to sort products by hand or map the FDA-assigned NDC number to another numbering system for automated procedures during data processing. The manufacturer responses will depend on whether their existing data systems are manual or automated, as well as the count of NDC numbers in their systems. In some cases, the incremental time required to sort products might justify switching to an automated sorting procedure. Given that only new NDC numbers would contain FDA-assigned product and package codes, the burden could increase over time as more products are introduced, and thus more manufacturers might switch from manual to automated systems over time. ERG assumed that most manufacturers would switch to an automated system (either immediately or eventually) and judged that manufacturers would need an average of 80 hours of an experienced programmer's time initially to assess the new requirements. Maintaining the mapping for new SKUs is estimated to require approximately 25 hours annually, assuming 100 new SKUs per manufacturer per year, 5 minutes to map each SKU to a new number, and 3 affected databases (e.g., databases maintained by different departments). Both estimates assume hourly pay rates of \$64 per hour based on 2003 Bureau of Labor Statistics pay and benefit rates for a senior-level computer programmer (BLS, 2003a; BLS 2003b). These judgments generate a first-year cost of \$5,120 and an annual cost of \$1,600 per manufacturer, as shown in Table 3-2. ERG assumed that all manufacturers would incur this cost

based on indications from manufacturers that the use of product and package codes as described above is a fairly common practice. The estimates were also reviewed and confirmed by an industry consultant.

### **3.2 Pharmacies**

Retail pharmacies, which would be generally exempt from the proposal, are most likely not affected by the change to the NDC numbering system because pharmacy processing systems typically do not use the internal NDC “intelligence” of product and package codes. Further, most pharmacy software vendors make any necessary changes to software for free as part of their normal mode of doing business. Thus, if pharmacies were affected in any way, the software would be revised for them at no additional cost.

Several industry contacts mentioned that due to pharmacists’ familiarity with certain product and package codes, some new errors might be generated. For example, a pharmacist might not recognize a dispensing error because he is no longer able to confirm the product’s identity based on his recognition of the NDC number. There is no means of confirming how often, if at all, this might occur.

While most pharmacies would not be affected by the proposed rule, large chain pharmacy stores were quite concerned. Some use the existing internal “intelligence” of the NDC number in building formularies for the adjudication of claims (adjudication refers to the process under which pharmacists submit claims for reimbursement from customer health plans). Building and maintaining formularies is usually done by a PBM or Medicaid. Increasingly, however, formularies of smaller plans (e.g., an employer work group’s healthcare plan) are managed by large chain pharmacy stores instead of PBMs. In some cases, the software used to build the

formularies for smaller plans makes use of the existing internal “intelligence” of the NDC number. This is an ongoing process, as formularies need to be maintained and formularies for new customers are continuously added into the adjudication processing network.

As one executive of a large chain pharmacy described, in building the formulary of a small health plan, the data entry staff will enter the NDC numbers of the requested drugs into the data processing software. “Wild cards,” such as an asterisk, are used to indicate that any number in the position of the wild card is acceptable in the formulary, and that the drug purchase is reimbursable. For many drugs, only 9 digits of the NDC number are entered and the last two digits are given as wild cards (under the compendium method of reporting NDC numbers with 11 digits instead of 10). This signifies that any package size for this product would be acceptable. Similarly, sometimes only seven or eight digits are entered and the rest of the NDC number is given as wild cards. This indicates (in those cases where the NDC product codes for a given product are sequential) that any strength or package size of that product is acceptable in the formulary.<sup>6</sup> Further, in some cases, only the first five digits (the labeler code) is entered and the rest of the number is given as wild cards. This signifies that any products by that manufacturer or labeler are acceptable in the formulary. In this way, data entry clerks can quickly add groups of products, saving data entry time. Respondents said that using the wild card saves substantial time.

Most of the uses of the wild card are unaffected by the proposed rule. With the proposed FDA assignment of the product code, however, the ability to sort formularies on the basis of product code (i.e., the ability to enter seven or eight digits and wild card the remainder of the

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<sup>6</sup> For example, when a new health insurance provider wants to add a product to their formulary (e.g., all strengths of Zestril by Astra-Zeneca), the company will add the first three digits of the product code (in this case, all strengths of Zestril begin with 013) instead of entering the complete NDC for every strength. The remaining digits of the product code and the package code, which vary with the product strength, package size or type, are entered as wild cards.

NDC number) would be lost. One executive estimated that he would need to add 4 people to his staff, as the loss of the wild card use would require them to manually enter every NDC for various strengths of the same product (Klimek, 2003). Other commentators questioned whether costs would generally be this high, but ERG lacks sufficient basis to make any other estimate. Thus, ERG assumed an average annual salary package of \$50,000 per individual and estimated ongoing annual costs for the additional labor at \$200,000 per year.<sup>7</sup>

The adjudication software provider facilitates the wild card use by providing the wild card capability in its software. This special feature, however, is not provided in most adjudication software. Based on the number of chain pharmacy customers for the adjudication software provider who offers the wild card capability, ERG estimated that about 10 percent of pharmacy chain stores at headquarters offices might incur this cost.

### **3.3 Pharmacy Benefit Managers**

As noted above, PBMs are usually the entities that build formularies and perform adjudication services. However, ERG judged that the wild card function is not a widely used by PBMs, based on discussions with an industry consultant (Winkelman, 2004). Among PBMs

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<sup>7</sup> The \$50,000 salary package was calculated using an annual salary of \$33,240 for a data entry operator, adding 38 percent for benefits, and rounding to the nearest \$10,000 (BLS, 2003a; BLS, 2003b).

contacted by ERG, a few predicted economic impacts similar to those described for chain pharmacy stores, while others foresee no economic impacts from the NDC change (Skaggs, 2003; Garcia, 2003).

ERG learned that the same provider of adjudication software for chain pharmacy stores also provides software for PBMs. The software used by PBMs includes a similar wild card capability for various pharmaceutical benefit management tasks. As noted earlier, however, wild cards are not a frequently used tool in the PBM industry. Thus, ERG assumed its use would be limited to the number of PBM clients of this software provider and estimated that 10 percent of PBMs will incur impacts under the proposed rule. ERG estimated that the PBM costs are likely to be similar to those of pharmacy chain stores, i.e., \$200,000 per year. Additional first-year costs are also likely as these companies adjust their operating procedures. ERG lacked reliable quantitative estimates of these costs, however, and judged them in any case to be modest relative to the ongoing costs of the additional data entry work. Also, additional first-year costs might substitute for and partially eliminate the recurring annual costs to the extent that the impacted firms can identify software solutions to avoid the additional ongoing data entry and processing work.

Changes to the adjudication process would be much more substantial if they impact or threaten to impact the very rapid point-of-sale processing of insurance claims by retail pharmacies. As the affected adjudication service companies modify their systems, they would attempt to ensure that point-of-sale processing speed is not affected. Thus, the adjudication service providers would undertake whatever software and Internet interface changes are necessary to avoid delays. Several executives mentioned the possibility of delays in electronic processing, but no definitive predictions were made that such delays were inevitable. One executive noted that the existing practice of using wild cards slows electronic data processing and that a software change that eliminates wild cards probably would not adversely affect data

processing speeds (Skaggs, 2003). The adjudication service providers could not provide estimates of any additional costs that they will incur to avoid such delays and no costs have been estimated here.

### **3.4 Other Potentially Affected Entities**

Other analysts of market information, whether employed by manufacturers or others, might make use of the internal “intelligence” of the NDC number in much the same way as do manufacturers. For example, drug industry marketing analysts might be interested in sales of particular product lines and at present can sort NDC data by product component in their analyses. These groups would lose some of this capability. Such a change, however, because it is not tied to routine, high-speed commercial transactions, probably does not generate significant impacts.

Compendium companies, hospitals, wholesalers/distributors, group purchasing organizations, state medicare agencies, and physician/dentist offices are not expected to be significantly affected by the changes to the NDC numbering system as described in the proposed rule.

Many contacts also noted that in various parts of the industry there are likely to be legacy systems in use that utilize the internal “intelligence” of the NDC numbers. Most of these systems have been developed to provide a shortcut for a processing activity. Given the random and infrequent use of these types of systems, however, ERG did not estimate any costs for these applications.

### **3.5 Aggregate Costs**

Table 3-2 also presents the aggregate costs over all healthcare sectors. The total first-year costs are estimated at \$3.8 million and the recurring annual costs at \$3.2 million.

**SECTION FOUR**

**ADDITIONAL COST IMPACTS OF  
PROPOSED REGISTRATION AND LISTING  
RULE PROVISIONS**

The proposed changes to the registration and listing rule will generate a number of small incremental costs for manufacturers, private label distributors, relabelers and repackagers, and other companies with pharmaceutical interests. This section examines the content of the proposed regulation paragraph by paragraph to reveal these costs. ERG's general conclusion is that the proposed rule will establish a series of minor new paperwork requirements, generating modest incremental costs.

The analysis was conducted using the draft regulation ERG received on December 15, 2004. Any changes to the draft made after this date are not reflected.

Table 4-2, at the end of this chapter, presents the paragraph by paragraph comparison of the existing and proposed registration and listing requirements. This section provides a quantitative examination of compliance costs for those provisions in Table 4-2 that have a discernible incremental cost that would not be offset by time savings of the electronic submission process. Some of the main considerations and judgments in analyzing the regulatory impacts are described below.

The cost impacts are divided into three major groups:

- Impacts occurring as a result of the need for all affected entities to apply for an NDC number, register their establishments, and list drugs electronically. These impacts also include costs created by the extension of requirements for

registration and listing to new groups of registrants and products. These costs are offset by reductions in the current costs of filling out registration and listing materials by hand, printing them out, copying them, and sending them to FDA by mail or courier.

- Impacts occurring due to a need to revise the labeling of certain regulated products.
- Impacts occurring due to the need for affected entities to set themselves up to register, list, and submit content of labeling electronically.

#### **4.1 Costs and Cost Savings for NDC Application and Recurring Electronic Submission**

This group of costs comprises the following categories (see Table 4-2), which are presented in detail in Appendix A:

- Costs for NDC numbers for new OTC, prescription, and API drug products.
- Costs for electronic submission of new product listings.
- Costs for electronic submission of changes to listings.
- Costs for drug salvagers to list.
- Costs to register new establishments electronically.
- Costs to review and update establishment registration electronically.
- Costs to certify no changes to listings.
- Cost to obtain user accounts from FDA.

These costs are more than offset by savings expected when paper submissions are replaced by electronic submissions, including reduction in time to submit product listings, make changes to product listings, and register new establishments. Appendix A shows the costs and

savings. Costs are estimated to be about \$3.9 million annually, and savings are estimated to be about \$7.7 million annually. Although the appendix shows the savings to greatly outweigh the costs, the estimates' wide uncertainty obliges ERG to assume that this portion of the costs of the proposal is simply offset by the savings of electronic submittal vs. handwritten listings, listing changes, and registrations delivered as hardcopies via mail or courier. These cost savings do not include the savings to FDA, which will experience significant time savings from decreased data entry time, less error checking, and fewer unreadable entries that must be corroborated with the listing entity. These benefits are discussed in more detail in Section Six.

Some manufacturers are concerned about time lags due to FDA assignment of product and package codes: many processes depend on the timely assignment of the NDC number, which manufacturers previously controlled. Manufacturers commented, however, that if FDA runs a real-time, computerized process for assigning NDC numbers, costs due to time lags would be negligible. FDA is planning to assign NDC numbers in a prompt manner.

Manufacturers also commented that, if this requirement is interpreted to mean that they must consolidate labeler codes across subsidiaries and separate operating divisions, significant additional costs will be incurred.<sup>8</sup> Many subsidiaries function separately from their parent companies regarding labeling decisions and this operation would now have to be consolidated with respect to NDC number assignment. Manufacturers could not estimate impacts, since many companies have never considered this step, but those impacts could be notable (Yadechevich, 2004; Cooksey, 2004). It is assumed that labelers will be able to keep one labeler code each and that FDA will not require them to consolidate all subsidiaries and divisions under one parent company labeler code.

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<sup>8</sup> However, because the FDA would be assigning the NDC, even if they share one labeler code, the subsidiaries and divisions would not have to coordinate on assigning the NDC.

## **4.2 Labeling Revision Costs**

Previously, FDA required that NDC numbers be obtained for finished and bulk pharmaceuticals and biologics subject to Part 207, but it was not required to appear on labeling. The proposed rule will change this. NDC numbers will be required to appear on all drug product, biologic, and API labels that are subject to Part 207.

Manufacturers of human and animal prescription drugs and biologics are mostly covered by the final barcode rule and place NDC numbers on their labels. Labeling conventions require manufacturers to present the NDC number in readable text under the barcode representation. Previously, NDC numbers were allowed to appear with an “N” or “NDC” prefix; now only the “NDC” prefix will be allowed. In the absence of concrete information, ERG assumed that 50 percent of prescription SKUs will require revision of the labeling to change the prefix. More effort will be needed for the prescription products that are not subject to the barcode rule, and there might be some other unforeseen issues with NDC numbers on some products. Also, relabelers and repackagers of prescription drug products that currently print the manufacturer’s or private label distributor’s (PLD’s) NDC number will need to revise their labels, regardless of whether the prefix is correct. Unapproved drug products and allergenic products that currently do not print NDC numbers on their labels will also be required to do so under the proposed rule. To account for these issues, ERG assumed that an additional 10 percent of prescription labels will need to be changed, for a total of 60 percent of prescription labels requiring changes. Previously, ERG estimated that there are 78,000 separate prescription SKUs based on NDC number listings

(ERG, 2003).<sup>9</sup> Thus, approximately 46,800 SKUs (based on the 60 percent estimate) would need to be relabeled.

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<sup>9</sup> Note that the number of SKUs is roughly equivalent to the number of products times the number of dosage forms, concentrations, and package sizes, so a count of SKUs will be larger than the number of product listings in FDA's Drug Registration and Listing System (DRLS).

Prescription drug manufacturers and relabelers and repackagers of prescription drug products will be given only 3 years to comply with the requirements of the proposed rule. Therefore, prescription drug manufacturers will likely incur an incremental cost for revising labeling on any product that is not revised as part of a regularly scheduled label change within the 3-year implementation period. To estimate this cost, ERG used the weighted label revision cost of \$1,568 per SKU estimated in the ERG *Final Report on the Impact of Final Bar Code Regulations for Drug and Biological Products* (ERG, 2003).<sup>10</sup>

FDA has examined a select number of NDA files and found that prescription product labels are revised as frequently as once a year. However, previous discussions with consultants indicate that revisions occur less frequently than in the OTC industry (ERG, 1999). To account for labeling that might be revised less frequently, ERG assumed that 75 percent of the 46,800 SKUs mentioned above revise labeling as part of a regularly scheduled labeling change, while a labeling revision cost will be incurred for the remaining 25 percent, or 11,700 SKUs. Therefore, at a cost of \$1,568 per SKU, the prescription industry (both manufacturers and relabelers and repackagers) would incur a total one-time cost of \$18.3 million to revise prescription drug SKUs, or \$2.6 million over 10 years at a 7 percent discount rate.

To estimate the cost of revising labeling on animal drugs (both OTC and prescription), ERG assumes that there are 2 products per animal drug manufacturing site and 2 SKUs per product (4,152 domestic sites \* 2 \* 2), or 8,304 animal drug SKUs. ERG also assumed that 75 percent of these SKUs (similar to prescription drugs) will be

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<sup>10</sup> Using the FDA/ERG labeling model (ERG, 1999), ERG estimated labeling costs per SKU by manufacturer size (small, medium, large, and generic) and label type (cartons, containers, or both). The costs were then weighted based on estimated distributions of manufacturer size and label type in the prescription industry to derive a weighted average label revision cost per SKU.

revised during their normal relabeling cycle. Thus, at a cost of \$1,568 per label change, animal drug manufacturers will incur a total cost of 2.0 million, or \$0.3 million annualized over 10 years and a 7 percent discount rate.

In the OTC industry it is estimated that only 30 percent of SKUs currently have the NDC number printed on the label (FDA, 2004). ERG judged, however, that the OTC industry would generally not incur incremental label revision costs under this requirement. With the long implementation period provided in the regulation for OTC drug products (i.e., 7 years), manufacturers will be able to incorporate NDC number changes into other labeling changes likely to be needed over time. Based on a previous study on pharmaceutical labeling, ERG estimated that virtually all OTC products have label revisions over any 6-year period. These changes are motivated mostly by marketing trends (ERG, 1999). Thus, at some point during the implementation period, manufacturers will be revising labels anyway. Given that ample space is usually available on OTC drug labels, however, and given the 7-year implementation period allowed for OTC drugs, this label change can likely be accomplished along with regularly scheduled labeling changes.

Industry contacts raised some concerns about the new label requirements as they apply to unit-of-use containers (e.g., blister packs) for OTC retail products. Most such unit-of-use containers are subject to the barcode rule and will have the barcode with NDC number printed on them. The small percentage that are not subject to the barcode rule are exempt because they are not marketed to health care organizations, such as hospitals. These containers will require changes to their labeling, but generally will not require changes to packages or to printing equipment and are of sufficient size to accommodate NDC numbers. Nevertheless, some packaging lines might need to be retooled to accommodate the changes (Cooley, 2005). Because the changes required to meet the proposal are somewhat more challenging than ordinary label changes (such as minor modifications to the “Drug Facts” section), and to account for the

possible need to retool printing equipment, ERG assumes that the cost of making a change to each portion of a blister pack will be incremental to and more expensive than routine label changes. It is estimated, therefore, that the cost to make these changes is 1.5 times the average label change, or \$2,352. Relatively few SKUs fall into this category. Based on discussions with a consultant, ERG assumes that approximately 5,000 SKUs might be affected in this manner (Cooley, 2005). Under these assumptions, the one-time cost is \$11.8 million, or \$1.7 million annualized over 10 years at a 7 percent discount rate.

APIs are not subject to the barcode rule because it covers finished pharmaceuticals only. Thus API manufacturers will need to print the NDC numbers on labels. API manufacturers do not typically print NDC numbers on labels (Cooley, 2005), ERG assumes that every API product would require labeling with an NDC number. It is further assumed that these labels are rarely redesigned. However, because some APIs are shipped with bills of lading that are prepared for each shipment and an NDC number can easily be added to these, it is assumed only 50 percent of APIs would have labels, for lack of better information. FDA's Drug Registry and Listing System (DRLS) indicates that 5,322 bulk drug substances are currently listed (Loebach, 2005b; Muller, 2005), of which 80 percent (4,257) are assumed to be domestic. Half are assumed not to carry labels, for a total of 2,128 APIs with labeling that will need changing as a result of the proposal. The total one-time cost of revising labeling is estimated to be \$3.3 million, at an annualized cost of \$0.5 million over 10 years at a 7 percent discount rate.

#### **4.3 Costs of Setting Up Electronic Submission of Registration, Listing, and Content of Labels**

The proposal will require firms, including final drug product (prescription and OTC drugs, both human and animal), API, and biologics manufacturers and relabelers and repackagers to register, list, and in some circumstances provide content of labeling electronically. FDA

specifies that certain software will need to be obtained. Most human prescription drugs and biologics are already subject to requirements regarding electronic submission of labeling contents (Federal Register 68, 2003). Firms that manufacture human prescription drug products and biologics thus are assumed to have acquired this software, trained personnel in its use, and implemented electronic submission procedures.

Most OTC and animal drug products are not currently subject to the COL electronic submission requirement and would not necessarily have the relevant software. Furthermore, since the content of labeling for human prescription drugs is handled as a part of the application process, the electronic submission requirement does not extend to relabelers or repackagers. Therefore, ERG assumed that relabelers and repackagers generally would not have the software in place. API manufacturers whose products are subject to FDA application procedures would have the software, but API manufacturers producing ingredients for OTC preparations might not. Because it is not known which API manufacturers might have software, the entire group is considered to need it. The assumptions and estimates needed to determine costs for manufacturers of OTC products, APIs, and animal drug products, as well as for relabelers and repackagers, are discussed below.

Some manufacturing firms produce both OTC and prescription drug products. These firms are assumed to have software in place. OTC-only manufacturers are considered affected by the electronic submission requirements. Although definitive statistics are not available, ERG estimates based on discussions with consultants that roughly 75 percent of drug product manufacturers make only OTC products (Cooley, 2005). The Census Bureau (2004) reports that 901 owner firms (the first level of establishment ownership) own establishments that

predominantly or secondarily manufacture finished drug products. Thus 676 firms (75 percent of the 901 firms) are assumed to need to purchase software.<sup>11</sup>

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<sup>11</sup> To avoid underestimating the number of affected OTC firms or the number of firms manufacturing prescription drug products as reported in Table 3-1, ERG did not adjust the number of firms to ensure consistency with the total number of firms reported by Census. As noted in Table 3-1, the count of 666 prescription drug manufacturing firms is believed to be an overestimate, since duplicate firms may have been missed.

The count of affected final product manufacturing firms for OTC products is based on Census Bureau counts of pharmaceutical industry firms. Census Bureau counts reflect the number of firms in the first level of corporate ownership for establishments earning more than \$100,000 in revenues from the manufacture of final drug products.<sup>12</sup> The Census count represents neither the number of sites, as registered in DRLS, nor the number of firms that are contained in the DRLS database. The DRLS data are known to contain duplicate firms, as well as entities subsumed in mergers and acquisitions that are still assigned active labeler codes (Loebach, 2005a). The database might also include firms whose drugs have not reached, or will never reach, commercial distribution, because an establishment must be registered shortly after an NDA application is made (Loebach, 2005a). Applying for an NDA indicates that a drug is on its way to being commercially distributed but does not guarantee that it will be commercially distributed. It is assumed that a firm directly owning the establishment or establishments that manufacture the final drug products will acquire the software, since products are not listed at the establishment level. The Census count is considered a reasonable estimate of the entities having products in commercial distribution and that might purchase the software.

Software is expected to cost each affected firm \$250. A training course for 2 people is estimated to cost \$150 (Federal Register 68, 2003). The two people are estimated to be trained at

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<sup>12</sup> Other counts of firms, such as those in the DRLS data or in the Orange Book, can count multiple levels of corporate organization in larger firms. A large corporation can include not only the ultimate parent company, but it can also contain numerous large subsidiaries, all considered separate firms, subsidiaries of subsidiaries (again, separate firms), and so on, down to the last level of the corporation, below which only establishments are found. The Census counts the immediate owner of an establishment. This owner may be a firm at the lowest level of the corporate structure—or it could even be the parent corporation, if the parent corporation is the direct owner of that establishment.

a cost of \$51.73 per hour for 6 hours each (fully loaded wage of mid-level manager; BLS, 2003a). The total per-firm cost is \$1,021, or \$145 over 10 years at a 7 percent discount rate. Given the number of affected OTC manufacturing firms and these per-firm costs, it is estimated that the setup costs for electronic submission would be about \$690,000 for a one-time cost or \$98,000 annualized over 10 years at a 7 percent discount rate.

All API firms are assumed to need to acquire software. Census (2004) reports that 342 firms own establishments that are predominantly involved in medicinal and botanical manufacturing, which generally encompasses API manufacturing (although some types of products would not fall under Part 207).<sup>13</sup> These 342 firms are assumed to obtain software and train employees in its use. The one-time cost is approximately \$350,000, and the annualized cost is about \$50,000.

All firms involved in manufacturing veterinary drug products are also assumed to need the software. Census data indicate 80 out of the 901 firms that own establishments that predominantly or secondarily manufacture pharmaceutical products manufacture veterinary use preparations. Although some of these might also produce human drugs, ERG assumed that all 80 would need to acquire software and train employees. These costs are estimated to be about \$82,000, or \$12,000 on an annualized basis.

Repackagers and relabelers must also acquire software and train employees. In a previous report, ERG estimated that there are 229 repackagers and relabelers that serve the pharmaceutical industry using Small Business Administration data from 1999 (ERG, 2003). ERG also recently consulted an industry expert who independently estimated that there are roughly 200 to 300 relabelers and repackagers in the U.S. (Cooley, 2005). Based on this data, it

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<sup>13</sup> A count of firms owning establishments that secondarily produce such products was not available.

was assumed that there are approximately 250 domestic relabelers and repackagers. ERG estimated that these firms incur a one-time cost of \$255,000, or \$36,000 on an annualized basis.

When all costs to each type of firm are summed, the total one-time costs are estimated to be \$1.4 million, and the annualized costs are estimated to be \$196,000.

#### **4.4 Costs of Continuing Submissions of Content of Labeling**

Additional costs might be incurred to submit the incremental content of labeling for a very small number of human prescription drug products and biologics, OTC products, and products managed by relabelers and repackagers. For those human prescription drugs without approved U.S. applications, the package inserts must be submitted electronically. The drug facts labeling for OTC drugs would need to be submitted electronically. For animal drugs, the manufacturer's identifying information and user instructions would need to be submitted electronically. Makers of APIs are not required to submit such information (FDA, 2005). Costs for submission for OTC firms and animal products firms are estimated below; ERG assumes that the costs of submission for the minimal number of human prescription drug products covered by the content of labeling rule are negligible.

The cost to acquire the software for electronic submissions is covered above. Costs for submissions are estimated based on the number of affected products (i.e., the number of products times the number of dosage forms or concentrations; COL submission is not triggered by package size differences). A count of SKUs includes the package size counts and is therefore too

large. For OTC products, ERG assumes that there might be two such COL submissions per listed product twice per year, on average, to account for multiple dosage forms or concentrations. ERG estimates that there 38,001 OTC products in the DRLS, of which 80 percent are assumed to be domestic (To derive the 38,001 OTC product listings, ERG applied the percentage distribution of OTC, prescription, and bulk listings (Loebach, 2005b) to the most recent total number of listings (Muller, 2005)).<sup>14</sup>

For animal products, FDA lists 2,076 domestic sites in DRLS (Loebach, 2005b). A count of veterinary products was not provided; ERG assumes that on average these sites manufacture 2 products. ERG further assumes 1.5 dosage forms/concentrations might be associated with each of these products, and again, 2 submissions per year would occur for these product/dosage forms.

Under an assumption that these submissions would entail 0.25 hours per submission per affected label, and a wage rate of \$51.73 (BLS, 2003a), ERG estimates that the annual costs of new COL submittals would be \$1.7 million (\$1.57 million for OTC products and \$0.16 million for animal products).

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<sup>14</sup> OTC drug products have the largest numbers of SKUs per product listing among the affected product types. ERG (2003), reports that there are about 98,639 OTC SKUs, which compared to the 38,001 OTC product listings in DRLS, indicates that there are roughly three SKUs per product listing. The number of dosage forms or concentrations, therefore, would most likely be less than three.

#### 4.5 Totals for Regulatory Costs

The additional provisions, including the NDC format changes covered in Chapter Three, generate first-year annualized costs of approximately \$4.9 million and other recurring annual costs of approximately \$5.8 million (see Table 4-1). These costs include the costs to relabel, to set up software and training for electronic submissions, and to submit COL. The costs associated with applying for NDCs, and those for the actual electronic registration and listing, are offset by the savings associated with going from a paper to a paperless approach, as shown in Appendix A. Nearly all of the first-year costs are accounted for by the need for prescription drug product manufacturers and relabelers and repackagers of prescription drug products to revise labeling on packages with correctly prefixed NDC numbers and the applicable NDC numbers (e.g., no PLD NDC numbers).

The total costs of the proposal, annualized over 10 years at a 7 percent discount rate, would be \$10.7 million per year.

**Table 4-1. Summary of Costs**

<b>Cost Item</b>	<b>First-Year Cost</b>	<b>Annualized First-Year Cost</b>	<b>Annual Cost</b>	<b>Total Annualized Cost</b>
Incremental Cost to Obtain NDC Number & Ongoing Electronic Submissions (See Appendix A)	\$0	\$0	\$0	\$0
Labeling Revision Cost	\$35,396,348	\$5,039,644	NA	\$5,039,644
Cost to Acquire Software and Train for Electronic Submissions	\$1,375,984	\$ 195,909	NA	\$195,909
Cost to Electronically Submit Content of Labeling	NA	NA	\$1,733,727	\$1,733,727
Intelligence Costs (from Chapter Three)	\$3,819,520	\$543,814	\$3,213,600	\$3,757,414
<b>Total Cost of Rule</b>	<b>\$40,591,852</b>		<b>\$5,779,367</b>	<b>\$10,726,693</b>

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		<b>\$4,947,327</b>		
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Table 4-2. Analysis of the Proposed Electronic Drug Registration and Listing System: Current and New Requirements

Section	Title	Current Requirement	Requirement Under New Rule (if different from current requirement)	Description of Incremental Cost Impact
<b>21 CFR Part 201</b>				
201.2 (a)	Drugs and devices; National Drug Code numbers	The NDC number is requested but not required on all drug labeling.	Drugs subject to the drug listing requirement of Part 207 must have the NDC number in human readable form, with the prefix NDC. No other NDC numbers might appear on the label but the NDC number of the last manufacturer, repackager, relabeler, or private label distributor responsible for the drug immediately before it gets to the wholesaler or retailer.	Incremental cost to print NDC number. Some cost to revise labels for drugs if any issues occur with NDC numbers currently in effect (considered rare). Some revised labeling costs for prescription drugs with "N" rather than "NDC" in prefix on label (common). Incremental costs for relabelers and repackagers to place their own NDC numbers on labels. Costs are estimated for these changes in Table 4-2. Adding NDC numbers to OTC drugs can be accomplished during regular label changes; no incremental costs for OTC drug relabeling.
201.25(e)	Can a drug that is not subject to the bar code requirement display a bar code?	None.	A drug product subject to Part 207 can display a bar code, but the barcode must then meet the criteria in the bar code rule.	No impact. Voluntary.
<b>21 CFR Part 207</b>				
<b>SUBPART A - GENERAL</b>				
207.1	Definitions	Existing section 207.3 currently has definitions.	Includes new definitions and slightly altered definitions from section 207.3 (also entitled Definitions).	No direct impacts. (The review has not addressed indirect impacts of changes to definitions.)
207.5	Purpose of this Part	None.	No requirements; only a justification for section 207.	None
207.9 (a)	Who is covered by this Part	None.	This Part applies to domestic manufacturers, repackagers, relabelers, drug product salvagers; not exempt under 510(g) of the Act or section 207.13.	Clarification. These groups are currently subject to Part 207. No cost.

207.9 (b)	Who is covered by this Part (continued)	None.	This Part applies to foreign manufacturers, repackagers, relabelers, and drug product salvagers; not exempt under section 207.13 (c) through (h).	Clarification. These groups are currently subject to Part 207. No cost.
207.9 (c)	Who is covered by this Part (continued)	None.	This Part applies to manufacturers of human biologics.	Clarification. These groups are currently subject to Part 207. No cost.
207.9 (d)	Who is covered by this Part (continued)	None.	This Part does not apply to establishments solely engaged in the recovery, screening, testing, processing, storage, or distribution of human cells, tissues, or cellular and tissue-based products. They must provide information as described in Parts 207.33(b)(3), 207.33(b)(4), 207.49(a), 207.49(c), 207.49(j)(2), 207.53(e)(2), 207.54(b)(6)(ii), and 207.55(a).	See Part 1271 in this table.
207.9 (e)	Who is covered by this Part (continued)	None.	This Part does not apply to owners and operators of human blood and blood product establishments. These must register and list under Part 607.	See Part 607 in this table.
207.9 (f)	Who is covered by this Part (continued)	None.	This Part does not apply to establishments that solely manufacture, prepare, propagate, compound, assemble, or process medical devices. These must register and list under Part 807 (or under 607, this is not clear due to edit in proposed regulation).	See Part 807 in this table.
207.13 (a)	Who is exempt from the registration and listing requirements	Pharmacies are exempt as long as they don't manufacture, repack, or relabel drugs other than what would be considered normal for the profession	The exemption does not apply to pharmacies that manufacture compounded positron emission tomography drugs.	Clarification. No cost.

		(see section 207.10).		
207.13 (b)	Who is exempt from the registration and listing requirements	Hospitals, clinics, and public health agencies are exempt (see section 207.10).	This exemption does not apply to hospitals, clinics, and public health agencies that manufacture compounded positron emission tomography drugs or those that hold a biologics application.	Clarification. No cost.
207.13 (c)	Who is exempt from the registration and listing requirements	Practitioners who are repackers and relabelers are not mentioned as exempt in section 207.10, but are understood to be included under manufacturers according to section 510 of the Act.	Practitioners who are licensed by law to prescribe/administer drugs and who manufacture, repack or relabel drugs for use in their practice are exempt.	None.
207.13 (d)	Who is exempt from the registration and listing requirements	Repackers and relabelers whose drugs are used solely for research, teaching, or chemical analysis are not mentioned as exempt in section 207.10, but are understood to be included under manufacturers according to section 510 of the Act.	Manufacturers, repackers, and relabelers whose drugs are used solely for research, teaching, or chemical analysis are exempt.	None.
207.13 (e)	Who is exempt from the registration and listing requirements	Repackers and relabelers of harmless inactive ingredients are not mentioned as exempt in section 207.10, but are understood to be included under manufacturers according to section 510 of the Act.	Manufacturers, repackers, and relabelers of harmless inactive ingredients are exempt.	None.
207.13 (f)	Who is exempt	Repackers and relabelers	Manufacturers, repackers, or relabelers	None.

	from the registration and listing requirements	of Type B or Type C medicated feeds are not mentioned as exempt in section 207.10, but are understood to be included under manufacturers according to section 510 of the Act.	of Type B or Type C medicated feeds are exempt, except for manufacturers, repackers, or relabelers of Type B or Type C medicated feeds made from Category II, Type A medicated articles.	
207.13 (g)	Who is exempt from the registration and listing requirements	Any manufacturer of a virus, serum, toxin, or analogous product intended for treatment of domestic animals who holds an unsuspended and unrevoked license (from section 207.10)	None.	None.
207.13 (h)	Who is exempt from the registration and listing requirements	Carriers, in their receipt, carriage, holding, or delivery of drugs in the usual course of business as carriers (from section 207.10)	None.	None.
<b>21 CFR Part 207</b>				
<b>SUBPART B - REGISTRATION</b>				
207.17 (a)	Who must register	Section 207.17 is a new section; similar in structure to the existing subpart C. Part 510 of the FDC Act requires manufacturers, repackers, and relabelers to register.	Drug product salvagers must register establishments in accordance with this Part.	Drug product salvagers are the manufacturers, or possibly relabelers or repackagers, who already register. No independent salvagers have been identified. Considered clarification. No cost.
207.17 (b)	Who must register	Section 207.17 is a new section; similar in structure to the existing subpart C.	Private label distributors must, unless otherwise exempt under section 207.13, register if they manufacture, repack,	PLDs that also manufacture, relabel, or repackage would already be registered as manufacturer, relabeler, repackager, or salvager as well as, possibly, PLD.

			relabel, or salvage drugs.	Considered clarification. No cost.
207.21	When must initial registration information be provided?	The owner or operator of an establishment entering into the manufacture or processing of a drug or drugs shall register the establishment within 5 days after the beginning of the operation and shall submit a list of every drug in commercial distribution at that time. [The existing Section 207.21 is more strict than what is specified in the new rule and includes rules for new owners and operators, timetables regarding renewals of registration, and updates of drug listing information. Also, in Subpart D, it is specified that each foreign drug establishment whose drugs are imported or offered for import into the United States shall comply with the establishment registration and drug listing requirements in subpart C of this part.]	None.	None.
207.25 (a)-(g)	What information is required for registration?	For each establishment, the registration number, the type of operations	In addition to current requirements, the name, address, telephone and fax numbers, and e-mail address of the	Incremental cost (small) for providing additional contact information. Considered offset by cost savings over time of electronic submission. See Appendix A.

		<p>performed, the name and full address of the drug establishment; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned, partnership or corporation); and the name of the owner or operator of the establishment. The term name of the owner or operator includes in the case of a partnership the name of each partner, and in the case of a corporation the name and title of each corporate officer and director and the name of the State of incorporation. The current requirement in section 207.25 is more restrictive in that it also specifies requirements for drug listing.</p>	<p>official contact, as provided in section 207.69, for each establishment; and with respect to foreign establishments only, the name, address, telephone and fax numbers, and e-mail address must also be provided for the U.S. agent and each importer of the drug.</p>	
207.29 (a)	Annual review and update of registration information	<p>Section 207.29 (a) is new; section 207.21 reports that owners or operators shall renew their registration information annually.</p>	<p>Owner/operator has to provide certification annually if no changes occurred during the year.</p>	<p>Incremental cost of certification if no change. Considered offset by cost savings over time of electronic submission. See Appendix A.</p>
207.29 (b)	Expedited updates	<p>Section 207.29 (b) is new; Section 207.26 requires that changes in individual</p>	<p>Manufacturers, repackers, relabelers, and drug product salvagers must update registration information no later than 30</p>	<p>Incremental cost of electronic updates to registration information.. Considered offset by cost savings over time of electronic submission. See Appendix A</p>

		ownership, corporate or partnership structure location or drug-handling activity, shall be submitted by Form FDA-2656 (Registration of Drug Establishment) as amendment to registration within 5 days of such changes. A change in a registered establishment's firm name within 6 months of the registration of the establishment is required to be supported by a signed statement of the establishment's owner or operator that the change is not made for the purpose of changing the name of the manufacturer of a drug product under Sec. 201.1 of this chapter.	calendar days after closing or selling an establishment, changing an establishment's name or address, and changing the name, address, telephone/fax numbers, or email address of the official contact or U.S. agent.	
<b>21 CFR Part 207</b>				
<b>SUBPART C - NATIONAL DRUG CODE NUMBER</b>				
207.33 (a)	What is the NDC number?	FDA currently assigns labeler code.	FDA will assign the complete NDC number to each drug that is subject to the listing requirement in this Part.	Possible loss of NDC number "intelligence" at the firm level as estimated in Section Three and presented in Table 4-2.
207.33 (b)	Who must obtain an NDC number	NDC numbers are required for all listed drug products.	None.	None.
207.33 (c)	What information	FDA currently requires	For active pharmaceutical ingredients,	Manufacturers will spend incremental time to submit

	<p>must a manufacturer submit before FDA assigns an NDC number</p>	<p>manufacturers to submit information about the active ingredients and requests but does not require information about the inactive ingredients. Manufacturers or private label distributors must provide information on their products.</p>	<p>the manufacturer must supply their name, address, telephone and fax numbers, email address, and labeler code, the drug's established and proprietary name (if applicable) and the package size and type and the Drug Master File, if one exists. In addition for a manufacturer's drug other than an active pharmaceutical ingredient, the name and quantity of each active pharmaceutical ingredient and the name of each inactive ingredient (unless approved application numbers are provided for either), the dosage form, the package size and type (including immediate unit of use containers), the drug's marketing status, the drug or drug product type and the size, shape, color, and code imprint, if any. In addition, manufacturers for private label distributors will need to submit the private label distributor's name, address, telephone and fax numbers, email address, labeler code, establishment registration number and the drug's proprietary name (if applicable).</p>	<p>information to FDA and obtain an NDC number instead of simply assigning an NDC themselves, although most of this information was previously required for listing anyway. Amount of incremental time will be affected by the efficiency of the FDA system for assigning an NDC number. Must also provide private labeler information. Small initial incremental costs for new NDC applications considered offset by costs savings over time of electronic submittals. See Appendix A.</p>
<p>207.33 (d)</p>	<p>What information must a repacker/relabeler submit before FDA assigns an NDC number</p>	<p>The information in the next column is currently required when registering and listing drugs</p>	<p>The repacker or relabeler has to submit their name, address, telephone and fax number, email address, labeler code, the NDC number assigned to the drug immediately before the drug is received by the repacker/relabeler, the type of operation performed for the drug, and the drug's established and proprietary name (if applicable). The repacker must also submit the package size and type,</p>	<p>New requirement for repackers or relabelers to submit information to FDA to obtain an NDC number. Incremental time needed will depend partly on efficiency of the FDA NDC assignment process. Repackers and relabelers must also provide private label distributor info. Information required, however, is similar to that required for listing. Listing information requirements would decrease because the information would be provided at NDC application. Small incremental cost for new NDC applications considered offset by cost savings over time of electronic submittals. See</p>

			including immediate unit-of-use container, if applicable. In addition, repackers and relabelers for private label distributors will need to submit the private label distributor's name, address, telephone and fax numbers, email address, labeler code, establishment registration number and the drug's proprietary name (if applicable).	Appendix A.
207.33 (e)	How must the information be submitted	See section 207.61.	See section 207.61.	See section 207.61.
207.33 (f)	What changes in the information will require a new NDC number	Currently update drug listing info twice a year. (Firms create NDC numbers themselves without FDA involvement.)	A new NDC number is required if there are any changes, with the exception of contact information.	Incremental cost of filing for a new NDC number. Considered minimal and offset by cost savings over time of electronic submittals. See Appendix A.
207.33 (g)	When must the manufacturer, repacker, or relabeler provide the information for an NDC number	Equivalent to current requirements for submission of drug listing information.	At the time drug listing information is required under Section 207.45 or 207.57.	None.
207.37	What restrictions pertain to the use of NDC numbers	Section 207.37 exists but is entitled inspection of registrations and drug listings.	Assigned NDC numbers cannot be used for a different drug. When marketing is resumed for a discontinued drug, the original NDC must be used, unless the drug is otherwise changed. The NDC number must not be used to denote FDA approval. The NDC number must not be used on products not subject to this Part.	None.
<b>21 CFR Part 207</b>				
<b>SUBPART D - LISTING</b>				
207.41	Who must list	Current section 207.20	Aside from manufacturers, repackers,	Incremental cost for drug product salvagers to list, although

	drugs	addresses the same topic.	relabelers, now drug product salvagers, who are subject to the registration requirements under § 207.17, must list their drugs being manufactured, repacked, relabeled, or salvaged for commercial distribution. If they engage in more than one activity, then they must provide the information requested in Section 207.49 and/or 207.53. Private label distributors only have to list their drugs if they manufacture, repack, relabel or salvage drugs.	these products would already be listed by the manufacturer, relabeler, or repackager, so the listing could be copied. Cost considered offset by cost savings of electronic submittals. See Appendix A.
207.45	When must initial listing information be provided	At the time of registration (see current section 207.21)	None.	None.
207.49	What listing information is required for manufacturers	Manufacturers must provide the NDC number; the drug or drug product type (human vs. animal); the route of administration of the drug, the approved application number of approved biologics license application number; the name, address, and registration number of each establishment where the drug is manufactured; the size, shape, color and code imprint for drug products subject to imprinting requirements; the schedule of the drug; and current labeling and samples of labeling/advertisements	Less information is required, since it is submitted with the NDC application. Additionally, manufacturers need to provide contact information on private label distributors and importers.	Potential incremental cost to provide additional information on private label distributors, where such information is not now being presented. Considered offset by cost savings over time of electronic submittals. See Appendix A.

		unless the approved application number is provided.		
207.53	What listing information is required for repackers and relabelers	Repackers and relabelers must provide the NDC number; the drug or drug product type (human vs. animal); the route of administration of the drug, the approved application number of approved biologics license application number; the name, address, and registration number of each establishment where the drug is manufactured; the size, shape, color and code imprint for drug products subject to imprinting requirements; the schedule of the drug; and current labeling and samples of labeling/advertisements unless the approved application number is provided.	Need to provide FDA-assigned NDC number. Need to provide contact information on private label distributors and importers. Some information requirements are dropped because the information is submitted with the NDC application. Must submit label and content of labeling (COL), only if changed from manufacturer's label or COL, if prescription drug or certain types of OTC drugs.	Incremental cost to provide additional information on private label distributors, where such information is not now being provided. Considered offset by cost savings over time of electronic submittals. See Appendix A.
207.54	What listing information is required for drug product salvagers who are not repackers and relabelers	None	For each drug they list (include those salvaged for private label distributors), the NDC number assigned directly before received by the drug product salvager, the lot number and expiration date of the salvaged drug product, the name, address, and registration number of each establishment where the drug	Incremental cost for drug product salvagers to list products. Cost should be minimal, since the same drugs would already be listed as manufactured, relabeled, or repackaged by the registrant and the listings could be copied for the relatively few drugs salvaged. Costs considered offset by costs savings of electronic submittals. See Appendix A.

			product salvager applies process controls to the drug or salvages the drug, with respect to foreign establishments only, the name address, telephone and fax numbers, and e-mail address of each importer of such drug in the United States that is known to the establishment, and of each person who imports or offers for import such drug to the United States, and if the drug is salvaged for a private label distributor, the name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor.	
207.55	What additional drug listing information might be required	For a particular drug product, upon request, the manufacturer, repacker, relabeler, or drug product salvager must briefly state the basis for its belief that the drug product is not subject to section 505 or 512 of the act or section 351 of the Public Health Service Act (this includes identifying some of the documents that provide evidence for this belief).	The specific documentation required is deleted.	None.
207.57	What are the requirements for reviewing and updating listing information	During each subsequent June and December, or at the discretion of the registrant when the change occurs, the following information must be submitted for any manufactured, repacked,	Very similar to the old requirements, except that only the expiration date of the last product manufactured has to be provided for discontinued product. Also, if no changes have occurred since the last review and update, certification is required.	Incremental cost of certification if no change. Considered offset by cost savings over time of electronic submission. See Appendix A.

		<p>re-labeled or salvaged drug: any new drug listings, any listings of drugs that have been discontinued (provide National Drug Code (NDC) number, the identity by established name and by proprietary name, and date of discontinuance), any drug listings previously discontinued which have now resumed (including the NDC number, the identity by established name and by proprietary name, the date of resumption, and any other information required by Sec. 207.25(b) not previously submitted), any material change in information submitted in this Part, and no report is required if no change has occurred</p>		
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**21 CFR Part 207**

**SUBPART E - ELECTRONIC FORMAT FOR REGISTRATION AND LISTING**

207.61	How is registration and listing information provided to FDA	Paper format or electronic format.	Registration information, information required for an NDC number, drug listing information and the content of labeling must be provided in an electronic format. Advertisement and labeling other than the content of labeling can be provided in a paper format. COL for prescription drugs is the package insert,	Incremental cost to convert COL to electronic format for minimal numbers of prescription drugs, most OTC drugs, and all animal drugs. (Nearly all prescription drugs and a few OTC drugs that have an approved U.S. application number do not need to submit COL). Costs are estimated in Table 4-2. Incremental cost to electronically submit other registration and listing information on an ongoing basis considered offset by cost savings of electronic submittals. See Appendix A.
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			for OTC, the drug facts label, and for animal drugs, the manufacturer identification and instructions for use.	
207.65	How is a waiver from the electronic format requirements requested	None.	Waivers can be requested if entity does not have an email address and access to a computer and internet service provider that can access the electronic registration and listing system. Requests must include a phone number and address where the entity can be reached.	Incremental cost to file a waiver, although it is unlikely any such waivers would be filed. No cost estimated.
<b>21 CFR Part 207</b>				
<b>SUBPART F - MISCELLANEOUS</b>				
207.69	What are the requirements for an official contact and a United States agent	No requirement for an official contact outlined; but contact information for a United States agent is required for foreign drug establishments and this agent must reside or retain a place of business in the U.S.	Similar to current requirements, except an official contact for each establishment must be designated if subject to the registration requirements for this part. Also, each foreign manufacturer, repacker, relabeler, and drug salvager must also designate a single U.S. agent, who may not be a mailbox, answering machine or service, or other place where the agent is not physically present.	Incremental cost to designate an official contact. Incremental cost to switch to a physically present foreign agent for foreign establishments that currently do not fulfill this requirement. Costs for foreign entities not estimated for this analysis.
207.77	What legal status is conferred by registration and listing	No legal status conferred by registration or listing.	None.	None.
207.81	What registration and listing information will FDA make available for disclosure	All registration and some listing information. Not disclosable information includes: information submitted as basis for determination that a drug is not subject to section 505	All registration and listing information except information submitted as basis for a determination that a drug is not subject to section 505 or 512 of the act, limited information considered confidential commercial information, and inactive ingredients considered trade	None.

		or 512 of the act, a list on a drug product's inactive ingredients, a list of drugs containing a particular inactive ingredient.	secret.	
<b>21 CFR Part 314</b>				
<b>APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG</b>				
314.81	Other postmarketing reports	Allows paper submission.	Requires electronic submission.	All drugs in NDA process must submit COL electronically, so no setup costs apply. Ongoing costs are considered a negligible incremental cost to the overall cost of applying for an NDA. No cost estimated.
314.125	Refusal to approve an application	Includes wording "or processed" when referring to how the drug is made.	Removed wording "or processed" when referring to how the drug is made.	None.
<b>21 CFR Part 330</b>				
<b>OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED</b>				
330.1	General conditions for general recognition as safe, effective, and not misbranded.	No requirement for NDC number on labeling.	Requires NDC number on labeling.	See section 201.2.
<b>21 CFR Part 514</b>				
<b>NEW ANIMAL DRUG APPLICATIONS</b>				
514.111	Refusal to approve an application	None.	FDA has the right to refuse an application if the drug is produced in an establishment that is not registered and not exempt from registration under section 510 of the act and Part 207.	None.
<b>21 CFR Part 515</b>				
<b>MEDICATED FEED MILL LICENSE</b>				
515.1	Medicated feed mill license	Includes reference to section 207.20 and 207.21.	Replaced with reference to Part 207.	None.

	applications			
<b>21 CFR Part 601</b>				
<b>LICENSING</b>				
601.2	Applications for biologics licenses; procedures for filing	None.	Holder of biologics license application must electronically report the withdrawal from sale of an approved biological product within 30 working days of the withdrawal.	Negligible incremental cost. Cost not estimated.
<b>21 CFR Part 607</b>				
<b>ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS</b>				
607.3	Definitions	None.	Blood and blood products definition is extended to include licensed biologic components used in the manufacture of a licensed device.	None.
607.7	Establishment registration and product listing of blood banks and other firms manufacturing human blood and blood products	Paper registration forms are obtainable upon request from CBER	Electronic versions of the paper form are also now available and can be submitted electronically.	None..
607.22	How and where to register blood product establishments and list blood products	Requires submission of paper forms to mailing address.	Requires electronic submission of registration form.	Negligible incremental cost. Cost not estimated.
607.25	Information required for blood product establishment registration and blood product listing	Have to include a list of blood products, including bulk product substances as well as finished dosage forms, which have not been included in any list previously submitted on	Took out this wording, but the general requirement remains the same.	None.

		Form FD-2250 (National Drug Code Directory Input).		
607.35	Blood product establishment registration number	Paper form is provided as evidence of registration and a permanent registration number is assigned; NDC numbering system is used to assign labeler code.	Paper forms and NDC numbering system are no longer addressed in this section.	None.
607.37	Inspection of establishment registrations and blood product listings	None.	Just rewording of the section.	None.
607.39	Misbranding by reference to establishment registration or to registration number	None.	Registration also does not mean that the products may be legally marketed.	None.
607.40	Establishment registration and blood product listing requirements for foreign blood product establishments	None.	Foreign establishment or U.S. agent shall report changes in U.S. agent name, address, telephone, fax, or email address within 30 days.	Negligible incremental cost. Cost not estimated.
607.65	Exemptions for blood product establishments	None.	New requirement that persons who engage solely in the production of any plasma derivative, such as albumin, Immune Globulin, or a bulk product substance register and list their products	None.

			(they are no longer exempt under Part 207).	
<b>21 CFR Part 610</b>				
<b>GENERAL BIOLOGICAL PRODUCTS STANDARDS</b>				
610.60	Container label	Have to submit the name, address, and license number of the manufacturer.	In addition to previous requirements, have to submit NDC number.	Negligible incremental cost. Cost not estimated.
610.61	Package label	Have to submit the name, address, and license number of the manufacturer.	In addition to previous requirements, have to submit NDC number.	Negligible incremental cost. Cost not estimated.
<b>21 CFR Part 1271</b>				
<b>HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS</b>				
1271.1	What are the purpose and scope of this Part	None.	None (just updating a reference to a previous section).	None.
1271.20	If my HCT/P's do not meet the criteria in 1271.10 and I do not qualify for any of the exceptions in 1271.15, what regulations apply	None.	None (just updating a reference to a previous section).	None.
1271.22	How do I register and submit and HCT/P list?	Outlines requirements for paper submission; electronic submission also allowed.	Requires electronic submission; must in be in accordance with Part 11.	Negligible incremental cost. Cost not estimated.
1271.23	How is a waiver from the electronic format requirements requested	New section.	Waivers can be requested if entity does not have an email address and access to a computer and internet service provider that can access the electronic registration and listing system. Requests must include a phone number	Negligible incremental cost. Cost not estimated.

			and address where the entity can be reached.	
1271.25	What information is required for establishment registration and HCT/P listing	None.	None (just replacement of phrases that refer to paper forms)	None.
1271.37	Will establishment registration and HCT/P listings be available for inspection, and how do I request information on registrations and listings	None.	None (just replacement of phrases that refer to paper forms)	None.

## **SECTION FIVE**

### **DISCUSSION OF REGULATORY ALTERNATIVES**

The regulatory alternative examined is the assignment by FDA of a fully randomized NDC number for new products. Thus, each time a new product enters the market, FDA assigns a random, 10-digit, unique NDC number to the product. Dashes between the labeler, product, and package code are eliminated. The existing “intelligence” of the NDC number, in which the labeler, product, and/or package code information can be interpreted and used in database programming, would be entirely eliminated. All other changes proposed in the rule would remain the same.

A number of healthcare sector representatives commented to ERG that this change would generate large incremental costs for their operations. Table 5-1 presents estimates of the first-year impacts of potential changes. The estimates should be considered speculative because very few healthcare industry representatives could provide even approximate quantitative estimates of the costs of accommodating a change in the NDC number. ERG has developed the estimates after assessing the various comments collected.

#### **5.1 Pharmaceutical Manufacturers**

As was noted previously, manufacturers use the various components of the NDC numbers to analyze rebate data. Market research departments also make use of the NDC number in performing various marketing and forecasting functions.



Table 5-1. Regulatory Alternative–Cost of NDC Number Changes for Affected Health Care Sector Entities (a)

Type of Entity	Establishments	Share of Estab. With Costs	Cost per Establishment		Aggregate Cost		Additional Comment
			First-Year	Recurring Annual Cost	First-Year	Recurring Annual Cost	
Pharmaceutical manufacturers	746	100%	64,000	\$6,400	\$47,744,000	\$4,774,400	A calculated cost for Medicaid rebate, market analysis, and other affected departments to map newly assigned NDC numbers to another number so that existing data processing tasks can continue. All vendors are expected to be affected. Does not include firms that only manufacture unapproved drug products.
Pharmacies	67,434	N/A	Modest, not quantified	Modest, not quantified	Modest, not quantified	Modest, not quantified	Per pharmacy costs based on assumption that vendors modify software and provide to pharmacies free of charge. Some initial retraining or reorientation costs were not quantified.
Pharmacy chain stores (headquarter offices)	25	100%	\$3,000,000	\$300,000	\$75,000,000	\$7,500,000	Costs based on information provided by chain store information technology managers (Klimek, 2003; Trip, 2003).
Pharmacy benefit managers (PBM)s	76	100%	\$3,000,000	\$300,000	\$228,000,000	\$22,800,000	Estimate parallels that for chain store pharmacy headquarters. Allocation intended to reflect large internal project involving reprogramming and quality assurance work.
Hospitals	6,116	N/A	Modest, not quantified	Modest, not quantified	Modest, not quantified	Modest, not quantified	Assumed to be largely unaffected by the change in NDC numbers. Any adjustments in pharmacy purchasing systems are assumed to be small.
Compendium companies	5	N/A	Not quantified	Not quantified	Not quantified	Not quantified	Some database systems are likely to be affected. No data were available on which to base costs, however.
Wholesalers/distributors	6,500	100%	\$64,000	6400	\$416,000,000	\$41,600,000	Calculated cost based on reprogramming of some systems, such as those related to the PDMA-related tracking of distribution agreements for authorized suppliers, many of which use NDC numbers.
Group purchasing organizations	701	N/A	Modest, not quantified	Modest, not quantified	Modest, not quantified	Modest, not quantified	Assumed to be largely unaffected by the change in NDC numbers. Any adjustments in pharmacy purchasing systems are assumed to be small.
State Medicaid agencies	50	100%	\$3,000,000	\$150,000	\$150,000,000	\$7,500,000	Allotment of \$3,000,000 per state to accommodate changes to reimbursement procedures and programming.
Physician offices	195,655	N/A	Negligible	Negligible	Negligible	Negligible	Very few physicians dispense medications from their facility. Automation of systems used is assumed to be unaffected by NDC change. Changes to the drug purchasing system are assumed to be negligible.
Dentist offices	116,494	N/A	Negligible	Negligible	Negligible	Negligible	Very few dentists dispense medications from their facility. Automation of systems used is assumed to be limited and

							unaffected by NDC change.
<b>Total</b>			<b>\$9,128,000</b>	<b>\$762,800</b>	<b>\$916,744,000</b>	<b>\$84,174,400</b>	

Full randomization is likely to require significant reprogramming of manufacturer database systems, given that the components of the NDC number (especially the labeler code) will no longer have any meaning. For example, manufacturers currently use the labeler code to ensure they are paying rebates on their products, not those of another manufacturer. Under the regulatory alternative, every NDC would have a different labeler code. Thus, a new data field for an internal number would have to be developed to compensate for the loss of “intelligence” in the NDC number (Winkelman, 2004). To account for the impact of full randomization, ERG estimated 1,000 hours for an experienced programmer paid at a rate of \$64 per hour to develop a solution so that data can continue to be processed in similar ways. Additional time will also be required to maintain the additional data field for new products. ERG estimated that ongoing maintenance would require 100 hours annually. These expenditures are included in the costs in Table 5-1. All manufacturers are expected to be affected by full randomization.

## **5.2 Pharmacy Chain Drug Stores**

ERG held discussions with the electronic standards work group of the National Association of Chain Drug Stores (NACDS) and with individual chain drug store executives. The work group includes executives of many of the largest national drug store chains with responsibilities for advancing and coordinating industry standards for electronic commerce.

The chain drug store executives noted that the NDC number is used in many electronic operating systems throughout their operations, and changes in how the NDC is assigned could produce a variety of changes in their operations. They noted that even some small previous changes in NDC numbers or other basic industry nomenclature had created unpredictable ripple effects throughout their companies. More than one executive noted that the full randomization would be far more difficult to address than the Y2K issue.

The elimination of the internal “intelligence” in the NDC was described as requiring both a substantial up-front investment in reprogramming of various industry software and potentially increased operating costs. Most executives could not give precise estimates of the scope of the programming changes that would be required because of the complicated and interrelated nature of numerous software programs used in the companies, although some judged the impact to be quite large. One operator of drug stores and supermarkets, however, estimated their costs to accommodate a change in the NDC number at \$3 million (Trip, 2003).<sup>15</sup> Another executive, as noted previously, commented that the wild card system that is used to save data entry time during the building of formularies, would be lost. He estimated that 4 people would need to be added to his staff to deal with the ongoing effect of the NDC numbering change. This estimate was made assuming the changes proposed in the rule. With full randomization, ERG is estimating that 6 people might needed to be added to the staff given that the ability to conduct searches on the labeler code or the 9 digits encompassing the labeler and product code, would also be lost. Assuming an average annual cost of \$50,000 (as estimated in Section 3.2) per individual, the ongoing annual costs are estimated at \$300,000 per year. Lacking any other quantitative estimates, ERG used the estimates of \$3 million in investment costs and \$300,000 per year in ongoing annual costs to represent the cost impacts for large chain store companies to respond to the change in NDC numbers. The headquarter offices of all large chain drug stores are assumed to be affected.

Several executives were familiar with the Canadian system of drug identification in which drug numbers are provided serially and have no internal information value (i.e., the system results in a numbering scheme similar to that embodied by the regulatory alternative). The executives noted that the Canadian system consistently required more routine data

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<sup>15</sup> While this estimate was based on full randomization of the NDC number, other assumptions, such as whether both old and new products would be fully randomized, were less clear.

processing work because the data tables created for software applications were more complicated.

Some executives stated that their shipping and distribution systems might also be adversely affected under full randomization. Some stores assign their own shipping numbers, but these might be tied to NDC numbers. The shipping and distribution systems might require adjustments although no clarity was given as to how and how much it would cost.

### **5.3 Pharmacy Benefit Managers**

As noted previously, a change in the NDC numbering system creates some of the same difficulties for PBMs as for chain drug stores. As for chain drug stores, some PBMs will need to modify software and/or face increase operating costs to adjust to the randomization of new NDC numbers.

As described for the data entry process for building customer formularies, some PBMs make use of wild cards to more quickly enter formulary lists and perform other pharmaceutical benefit management tasks. Currently, some PBM software relies on only the first 9 digits (what they refer to as the “core numbers”) of the NDC number because they are not concerned which package size is purchased. The current “intelligence” in the NDC number shortens the data entry tasks by allowing the software to automatically enter a portion of the relevant number and then “wild card”, using an asterisk or other symbol, to represent any other number. Under full randomization, companies would need substantial reprogramming of these databases. Further, after the NDC change, data entry work would be more time consuming because IT staff would require more time to build the customer health-plan-specific data tables that are incorporated into their software.

One executive stated that a change in the NDC number, such as full randomization would be extremely difficult to accommodate and would require a thorough reevaluation of data entry and data processing methods (Skaggs, 2003). The reevaluation and software modification effort would involve this company and their principal software vendor because of the close interaction of the firms for claims adjudication services. While the executive was confident that a software solution could be found, she could not estimate how costly the changeover to a revised processing approach would be. In lieu of developing a software fix, this executive judged that the company's claims adjudication services would be severely impacted.

In lieu of more precise estimates, ERG expects that the PBM adjustment to a changed NDC numbering system would result in impacts similar to those predicted for the chain drug stores. All PBMs are expected to be affected. The distribution of costs between one-time software costs and ongoing annual costs is particularly uncertain, however. Industry executives cannot yet forecast whether software changes could reduce the additional ongoing data entry tasks that would result under the regulatory alternative.

#### **5.4 Pharmaceutical Wholesalers**

Wholesalers and distributors reported to ERG that they use the embedded "intelligence" of the components of NDC numbers in shipping and inventory activities. The Prescription Drug Marketing Act (PDMA) requires distributors to maintain documentation of their authorization to distribute products of specific manufacturers. Thus, a wholesaler will review purchases by a specific pharmaceutical manufacturer to determine whether it is an authorized distributor for that company. Partly for this reason (and also for many possible billing and other administrative reasons), wholesalers will sort sales records by manufacturer. Thus existing software to sort sales or shipment records by manufacturer is often dependent upon the components of the NDC

number. Industry contacts were uncertain whether other software functions in their companies also might utilize other components of the NDC number.

An executive in charge of automation systems at one wholesaler said that there would definitely be software impacts on his company, although he could not provide detailed estimates. He stated that a number of the firm's internal programs would need to be revised if the NDC assignment number was changed. These programs include programmed logic to read and correctly interpret the different formats for NDC numbers (i.e., 4-4-2 and 5-3-2 formats and others). ERG judges that while such programs are not integral to operations, they are probably widely used among wholesalers to compile manufacturer-specific data. The executive also stated that numerous other software systems might be dependent upon the components of the NDC number but he lacked complete information on this possibility.

ERG allocated 1,000 hours to reprogramming costs to represent the change in wholesaler/distributor operations. This number is based on discussions with an industry consultant and ERG's professional judgement that the reprogramming required will be a very complex undertaking. However, given that no one has been able to give an estimate of the number of hours required, it should be noted that this estimate could vary widely. At \$64 per hour, the reprogramming cost is calculated at \$64,000. ERG also estimated an ongoing cost, to map the NDC number of new products to an internal number. ERG estimated 100 hours a year for this task, given that wholesalers deal with multiple manufacturers.

## **5.5 State Medicaid Programs**

Computer software systems used in administering state Medicaid programs make extensive use of components of the NDC number. According to one state official, the logic of existing software programs would have to be changed. The loss of labeler code "intelligence" in

particular would require significant reprogramming and was described by a consultant as a tremendous cost burden (Winkelman, 2004).

Many state Medicaid programs use the services of software vendors, such as ACS State Healthcare, Unisys, and FirstHealth. If the NDC reassignment number were to be changed, these vendors would presumably prepare updates or modifications of existing software. According to the pharmacy electronic standards group, however, each state Medicaid program has distinct administrative elements and each state's changes would include unique elements.

Similarly, the Center for Medicare and Medicaid Services (CMS) quarterly reconciliation reporting system is dependent upon the labeler code for calculating the appropriate manufacturer rebate payments. This was also mentioned by other state Medicaid agencies as the primary use of the components of the NDC number.

None of the state personnel interviewed could assess the possible costs of changes to their operating systems. Nonetheless, ERG allocated \$3,000,000 per state for first-year costs to reflect the substantial restructuring of the large Medicaid reimbursement system. This estimate reflects that each state's Medicaid program will likely be impacted at a similar magnitude to chain drug stores.<sup>16</sup> Given the need to continually update numbers of new products, ERG also allotted 5 percent of first year costs to maintain the system.

## **5.6 Other Potentially Affected Entities**

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<sup>16</sup> Tripp (2003), an operator of drug stores and markets, estimated that it would cost their company \$3 million to accommodate full randomization of NDC numbers.

**Pharmacies and Pharmacy Software Vendors.** Some vendors of pharmacy automation systems and software criticized full randomization as requiring substantial changes to automation systems and software, as well as possibly other pharmacy operating practices. The software concerns focused primarily on the software used in the pharmacists' area (typically in the rear of the drug store), including software for scanning equipment and point-of-sale (POS) systems, and capabilities for electronic submission of Medicaid claims. Other vendors saw no problems or cost increases with the NDC numbering change. The differences in perspective appeared to be related to differences in the database architecture used to build the software.

Pharmacy software can include logic that is partly based on the components of the NDC system, such as a wild card system that allows searches on a partial NDC number to find groups of products. One executive expressed concern that a large number of pharmacies would need to modify their software to accommodate randomly assigned numbers. Overall, this vendor predicted that modifications would be substantial, and pharmacists would also need some retraining for automation-related tasks.

For example, some pharmacies use a hand-held scanner to acquire the NDC number and communicate it to various pharmacy software modules. The software search logic uses the NDC number in determining the specific product and the package size and type. Thus, the manufacturer and product code verify the manufacturer and product and the last two digits separately verify the source package for the medication. Some observers judged that this software would need to be reprogrammed to search a much larger database of random numbers than is necessary at present.

Other vendors of pharmacy software disagreed with these forecasts, however, stating that their pharmacy software systems would only be somewhat affected by full randomization in NDC assignment systems. For example, one vendor of point-of-sale software stated that their software did not use the components of the NDC number and therefore could accommodate a

random assignment of numbers for new products. The vendor stated that his pharmacy customers would need to relearn certain data operations, however, and might create some “work-arounds” to continue generating some of their data. The vendor also stated that the product updates they supply to customers would include modest modifications to ensure the most efficient interface among pharmacy systems. Further, he noted that pharmacists might occasionally want to sort their sales or inventory data by manufacturer, such as when there are class-action lawsuits against specific manufacturers. Overall, however, the vendor forecast that such changes would only arise occasionally and might cost pharmacies no more than a few thousand dollars each.

This vendor also forecast that some changes to 3<sup>rd</sup> party billing protocols would be needed under a new NDC system. While this point suggests some software changes for pharmacies, the vendor stated that only modest changes would be needed for his customers and that other changes in electronic data submission formats agreed to among industry groups have had greater impacts.

Pharmacists might also use the components of the NDC number in reviewing their inventories and removing expired products from their shelves. For this task, the manufacturer/labeler number can help pharmacists sort medications by manufacturer. The expired medications are then returned to manufacturers for credit.

Some pharmacies use contractor services to remove expired products from their shelves and return them for credit from the manufacturers or wholesalers. One such contractor reported that their software systems did not use the components of the NDC system and the firm did not foresee any significant impacts from a change in the NDC assignment system.

The executives noted that their pharmacists have considerable knowledge of the existing NDC numbers and that this is frequently of value for routine pharmacy operations. This knowledge might be useful in any number of ways (double-checking prescriptions, stocking and

inventory functions, and so on) that would be very difficult to quantify. Randomly assigned NDC numbers would never be useful in the same manner.

Overall, while some adjustments to pharmacy operations would be made, ERG did not assign costs directly to pharmacies or to software vendors. Pharmacies will need to make some adjustments but, in general, revised software is likely to be provided to them by vendors. The vendor costs were judged to be part of their normal cost of doing business for those who are affected. If revisions required are beyond the scope of normal changes to the software, pharmacy software vendors will likely pass costs on to pharmacies. Not enough data was available, however, to quantify these costs.

**Hospitals.** Executives at the American Society of Health-System Pharmacists' foresee no significant impacts for hospital pharmacies from a change in the NDC number assignment system. They judged that the several hospital pharmacy computer systems do not use the components of the NDC system in their software. They noted that hospitals would often have a computer system and software provided by their wholesale supplier (Thompson, 2003; Scheckelhoff, 2003). If the wholesale supplier needed to revise its software, it would do so and replace the software employed in their deployed systems in hospitals.

For tracking drug costs, hospitals rely on the "J-Codes" which are part of the Hospital Common Procedure Coding System (HCPCS) issued by the Center for Medicare and Medicaid Systems (CMS). Hospitals are mainly concerned with how J-codes interact with their billing code systems and administrative systems. J-codes are not product package specific but represent medication codes applicable to the medication data appropriate for hospital billing.

The use of NDCs in hospitals was recently examined by the National Uniform Billing Committee (NUBC) as reported in a statement before the National Committee on Vital and Health Statistics in February, 2001 (Arges, 2001). The NUBC is a data content committee that

evaluates the potential need for and use of data of various types in institutional healthcare settings. In general, NUBC found that the NDC numbers were used mainly in purchasing and that hospitals were mostly reliant upon J-codes for data reporting systems. NDC numbers are highly imperfect for their billing needs. NDC codes are largely undefined, for example, for the numerous intravenous solutions compounded by hospital pharmacies and therefore cannot be used for billing. NUBC estimated that the hospitals would require at least \$200,000 to implement a new data set (e.g., NDC numbers) for purchasing into their information technology systems, and to retrain staff in new data code uses. For this analysis, however, it should be noted that neither the proposed rule nor the regulatory alternative would require hospitals to incorporate NDC codes into their drug-related administrative systems. Thus, no costs are assigned to hospitals.

**Compendium Companies.** Compendium companies commented principally on impacts to their customers, i.e., users of NDC and drug price information. (While compendium companies themselves are not likely to be impacted by a change in the NDC numbering system, they would still be essential to the distribution of drug price and other related information to commercial entities.)

Compendium company officials noted that a substantial number of their customers maintain 9-digit rather than full 11-digit drug databases (e.g., PBMs), omitting the package size/type indicator at the end of the NDC number. Such customers are interested only in the medication types and not in reimbursement issues, making the package size/type indicator irrelevant for their purposes. While the compendium companies (and other data processing specialists) recommend against building databases in this fashion, the compendia have no control over their customers' use of their data. No data are available on the number of 9-digit databases in use. Full randomization would require such databases to be completely overhauled, as organizations with 9-digit databases would not be able to identify drug products for their formularies.

Some database systems, however, will not be affected, even under full randomization. Impacts on the healthcare data infrastructure will be smaller to the extent that entities use the entire existing NDC numbers as mere pointers to database information, without also using components of the NDC or UPC numbers (i.e., the manufacturer/labeler or product identifier) for data processing purposes. Many information technology specialists in the healthcare industry recommend building databases that use NDC-type identifiers only as pointers to database information. Nevertheless, the existence of fairly interpretable manufacturer/labeler numbers on drug products allows for some use of the information. It appears probable that at least some data users make use of the NDC number components.

ERG did not assign any costs directly to the compendium companies. While such organizations will definitely need to adjust to the NDC changes, ERG lacked a basis on which to quantify the cost impacts.

**Group Purchasing Organizations.** Given that pharmacy purchasing systems are expected to be largely unaffected, ERG also does not anticipate any major costs for group purchasing organizations. Any changes that need to be made to the software used by group purchasing organizations would likely be incurred as part of regular business costs by the vendors providing the software.

**Physicians and Dentist Offices.** While prescribing activities begin in physicians' and dental offices, the NDC changes are unlikely to impact these operations directly. Those physicians that use Computerized Physician Order Entry (CPOE) systems might find that their clinics or practices need to invest in software modifications to accommodate NDC numbering changes, but this is uncertain. Most "search" strategies for such systems are likely to be alphabetic rather than numeric (i.e., NDC-based) systems. No costs were attributed to these offices.

## **SECTION SIX**

### **BENEFITS**

This proposed rule will provide a number of benefits. First, there will be some cost savings to industry, which have been estimated and used to reduce the costs of the rule where similar actions will be taking place following promulgation that are less time consuming than those actions currently taking place (see Appendix A).

Second, there will be significant costs savings to FDA, since direct electronic submission will eliminate the need for FDA to enter the data, check it, and clean it before uploading the data into DRLS. Some checking of data will continue to occur, but, nevertheless, this time savings to FDA is significant. ERG has not estimated the cost savings associated with this benefit.

Third, the intelligence FDA obtains from the electronic submittal of COL is very valuable to the agency, and to the nation at large, by allowing FDA to rapidly search through information should any need arise. Such a need might arise, for example, during a bioterrorism attack, when a quick search of COL might provide drugs useful in counteracting such an event. ERG has not estimated a monetary benefit for this category.

## **SECTION SEVEN**

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## **APPENDIX A**

### **ASSESSMENT OF COSTS AND COST SAVINGS ASSOCIATED WITH THE ELECTRONIC SUBMISSION OF NDC APPLICATIONS, REGISTRATIONS AND LISTINGS**

Table 4-2 in Chapter Four identifies a number of paragraphs that would impose incremental costs on manufacturers, salvagers, relabelers, and repackagers to obtain NDC numbers, register establishments, and list products. Currently, aside from obtaining NDC numbers, these entities do register establishments and (except for salvagers) list their products; this can be a fairly time-consuming procedure involving the types of forms used for submitting data that will be entered into computer systems. These forms have spaces marked out for various data to be entered, one number or letter per space. The form has the product name at the top, with lines available to list all dosage forms, concentrations, and package sizes in which the product is available. The form must be filled out by hand and any changes to information that must be submitted to FDA require that the entire product form be redone, or at least an entire line of the product form to be redone—even if, for example, only the information on one product package size had changed from a count of 25 to a count of 30.

With electronic submissions, the information can be keyed in and any changes can be made to a copy of the form, allowing the submitter to make only the change that needs to be made. The entire form does not have to be filled out again if a number of changes needed to be made, nor would an entire line need to be redone if only a small change is necessary. Implementing an electronic system thus produces substantial time savings, particularly for listing changes.

Section A.1 discusses how the costs of the proposal are calculated for nine cost categories. Section A.2 presents similar information on the costs to register establishments, list

products, and make changes to the product lists under the regulation as it now exists. Section A.3 compares the costs and the cost savings.

#### A.24\_ Costs of Obtaining NDC Numbers, Registering Establishments, and Listing Products

In estimating the costs to obtain NDC numbers, register establishments, and list products under the proposed rule, ERG broke the costs into nine categories. Generally the costs are based on the number of product listings that appear in FDA's DRLS database. Each product listing currently begins as a paper sheet on which a product type is defined (e.g., acetaminophen); and within this product category, the concentration and dosage form is reported (e.g., 81 mg. tablets), as well as a package size or sizes for each concentration or dosage form (e.g., 30 tablets). For an OTC or prescription product, this combination of product and concentration/dosage form/package size makes up an individual SKU, so the number of NDC numbers under a product code will generally (under the proposal) equal the number of SKUs associated with the product. A product listing, therefore, may have one NDC number associated with it or it could have dozens. On average, perhaps three NDCs per listing might be needed based on the number of product listings and the number of SKUs estimated to be on the market (ERG, 2003) (see also Chapter Four). Because all manufacturers, relabelers, and repackagers must list their regulated products, the count of product listings represents all of these affected entities and their products (including prescription drugs, OTC drugs, APIs, and biologics).

**Cost Category 1—NDC numbers for new products.** To determine the average number of new NDC numbers that might be applied for each year, ERG used the FDA DRLS estimate of the average number of listings submitted per year (13,821) (Loebach, 2005c). ERG then adjusts these figures to account for foreign listings (no costs to foreign firms are calculated in this analysis). According to FDA, 80 percent of registered sites are domestic, so it is assumed that 80 percent of listings are domestic as well (Smith, 2004). Thus 11,057 new domestic listings are calculated.

The time required to submit information electronically and coordinate with FDA for an NDC number is estimated to be 0.5 hour per product (incremental to the time required for a firm to assign NDC numbers to themselves, as is currently done), with approximately three dosage forms/concentrations/package sizes associated with each product, each of which requires an NDC number.<sup>17</sup> This time involves typing the information required to be submitted to FDA onto an electronic form. The form would then be submitted electronically. It is assumed that FDA would respond fairly quickly to the request for an NDC number, leading to no delay in obtaining and using these numbers.

At a wage rate of \$51.73 (for a mid-level manager; BLS, 2003a), the total cost for this activity is estimated at \$285,984 annually (see Table A-1).

**Cost Category 2—Costs for electronic submission of new product listings.** A total of 11,057 new products are expected to be listed each year, as discussed above. Each listing is assumed to comprise an average of three dosage forms/concentrations/package sizes. The estimated time to transfer data to FDA's electronic forms and submit them is 1 hour, which leads to an estimate of \$571,968 to perform this task annually (see Table A-1).

**Cost Category 3—Costs for changes to listings.** FDA estimates (Loebach, 2005c) that approximately 22,568 updates are made to listing information, twice a year. Of these, ERG estimates 80 percent are domestic listing changes (as discussed above), for an estimate of 36,109

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<sup>17</sup> Note that it is assumed that the time required to pull together all of the necessary information is currently being done at the listing stage, and nearly the same amount of time to pull together information required to list a product is needed to pull together information to obtain an NDC number. Therefore, no incremental time is allotted to account for pulling together information either here or at the listing stage under the proposal.

domestic listing changes per year. ERG estimates that changes to a listing would entail 30 minutes using electronic listing forms. The cost estimated is \$933,954 (see Table A-1).

**Cost Category 4—Costs for salvagers to list and withdraw.** It is believed that salvaging is uncommon. About 5 percent of all products listed might be salvaged in any one year (Cooley, 2005), which leads to an estimate of listings of salvaged products totaling 4,182.<sup>18</sup> Since the original manufacturer generally salvages the product (Cooley, 2005), it is assumed that the product listing for the salvaged drug is available electronically and can be copied to produce the salvaged drug listing. ERG assumes that only 10 minutes will be spent submitting each listing on which a product type is noted as salvaged (salvagers can notify FDA that they will discontinue the product at the time of listing and thus no additional time is calculated for product withdrawal). The total annual cost of listing salvaged drugs is estimated to be \$36,055 (see Table A-1).

**Cost Category 5—Costs of registering new establishments.** According to FDA's DRLS, an average of approximately 1,128 sites are registered annually (Loebach, 2005c). Of these, 80 percent are assumed domestic, for a total of 902 sites. ERG assumes that about 1 hour is needed to fill in the electronic form registering a new site and submitting it to FDA. The cost of electronic submissions of new sites is estimated to be \$46,681 (see Table A-1).

**Cost Category 6—Costs to review and update registrations.** Under the proposed rule, registrants must review and update all their registration data annually. According to FDA's DRLS, 12,137 are currently registered (Loebach, 2005c). Of these, 80 percent are assumed

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<sup>18</sup>According to FDA DRLS data (Muller, 2005), the total number of product listings is 104,548. If 80 percent of these are assumed to be domestic, this produces an estimate of 83,638 domestic listings currently in DRLS. Five percent of 83,638 is 4,182.

domestic, for a total of 9,710 sites. ERG assumes that about 30 minutes will be required to review and update registrations resulting in a cost of \$251,139 for these sites (see Table A-1).

**Cost Category 7—Costs to for expedited updates.** In addition to reviewing and updating registrations, sites must also input some changes within 30 days. Based on the number of amendments made to registrations made in 2004 (Loebach, 2005c), ERG estimated that there would be 1,537 expedited updates annually (1,921 total expedited updates, of which 80 percent are domestic) and that each will take approximately 15 minutes. The total cost for this activity is estimated at \$19,875.

**Cost Category 8—Costs to certify no change.** The total number of listings that might need to be certified as having no changes is estimated to be 131,072 based on FDA DRLS data (81,920 June and 81,920 December reviews, multiplied by 80 percent to reflect only domestic listings). The amount of time needed to certify that a listing has not changed is expected to be small, perhaps about 15 minutes. The cost associated with certification is estimated to be \$1,695,089 (see Table A-1).

**Cost Category 9—Costs to obtain FDA user accounts.** Prior to the accepting electronic registration and listing information, a manufacturer, relabeler, repackager, or drug product salvager will have to obtain a user account from FDA to authenticate entry into the system. FDA would contact each manufacturer, relabeler, repackager, and drug product salvager and request that they provide electronic contact information to establish an account. It is expected that fulfilling this request may take approximately 15 minutes. FDA estimates that approximately 8,343 such requests would be made (based on the number of primary registrants in the FDA DRLS). ERG estimates that 80 percent of these (6,674) are domestic. The total cost for this requirement is estimated to be \$86,317.

**Total costs.** The total costs of NDC number applications and electronic registration and listing is estimated to be \$3,927,062 on an annual basis.

## **A.2 Cost Savings Associated with Electronic Submission of Registration and Listing Information**

Currently, manufacturers, relabelers, and repackagers must register establishments, list products, and make changes to their product listings. Each of these cost categories is discussed below with respect to an estimate of the cost to perform these tasks currently, using the paper system that is in place now.

**Costs for submitting product listings.** Each of the 11,057 domestic product listings estimated above is assumed to take 2.5 hours to compile, copy, and mail to FDA, since each one must be filled out by hand. This number is based on the existing estimate of 2.5 hours for preparing and mailing FDA Form 2657 (listing form) already approved by OMB under OMB Control Number 0910-0045. The cost is estimated to be \$1,429,921 (see Table A-1).

**Changes to listings.** Because the listing form must be redone every time a change is made, it is also assumed that 2.5 hour are needed to submit changes to listings. Based on the number of changes (36,109) estimated to be submitted annually (as discussed above), this cost is \$4,669,771 (see Table A-1).

**Costs for registering new establishments.** OMB already has approved an estimate of 2.5 hours for preparing and mailing FDA Form 2656 (registration form) under OMB Control Number 0910-0045. Using this estimate and the estimate of new domestic establishments registered each year derived previously (902), ERG estimates the annual cost of this task to be \$116,703 (see Table A-1).

**Costs for resubmission and amendments to registration.** Sites currently have to resubmit Form 2656 annually and submit amendments within 5 days. Based on the number of currently registered sites (12,137) and changes to registration forms (1,921), of which 80 percent are assumed domestic, ERG estimates that 11,246 such submissions occur annually ( (12,137 sites + 1,921 changes)\*0.80). Assuming that these resubmissions and amendments require 2.5 hours to prepare and mail, as estimated previously, ERG estimates the annual cost of this task to be \$1,454,441 (see Table A-1).

**Total costs savings.** The total costs of the current approach to registration and listing is estimated to be \$7,670,835 (see Table A-1). These costs will be replaced by the costs estimated for the proposed electronic submission process, and thus can be counted as cost savings or cost offsets.

### **A.3 Comparison of Costs and Cost Savings**

ERG estimates that it now costs manufacturers, relabelers, and repackagers of the range of regulated products approximately \$7.7 million to comply with registration and listing requirements. When the proposal becomes effective, ERG estimates that the same entities will incur costs of \$3.9 million. Because these estimates are not certain, it is only assumed that for these categories of costs, the savings experienced when firms switch from paper submissions to electronic submissions of registrations, listings, and changes will balance the incremental costs to obtain NDC numbers for new products, make additional certifications, list salvaged drugs, and, register establishments, and list products for groups of newly regulated products.<sup>19</sup>

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<sup>19</sup>It should be noted that ERG also considered costs incurred under the proposed rule due to waiver requests, public disclosure exemption requests, and annual report revisions for NDC numbers but that the costs associated with these tasks are expected to be negligible. Furthermore, while there may be some slight increase in

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costs for establishments that list and register drugs under 21CFR part 607 and part 1271, these are also expected to be negligible given that most of these establishments are already registering electronically.

**Table A-1. Comparison of the Costs to Register and List under the Current Regulation with Costs to Obtain NDC Numbers, Register, and List under the Proposed Regulation**

Cost or Cost Savings Item	Hours	Number Affected Annually (Listings or Establishments)	Total Hours	Hourly Wage	Total per Year
<b>Annual Cost Savings (costs of current regulatory requirements)</b>					
Submit new listing (all regulated products)	2.50	11,057	27,642	\$51.73	\$1,429,921
Submit changes to listings (includes withdrawals)	2.50	36,109	90,272	\$51.73	\$4,669,771
Submit new registrations	2.50	902	2,256	\$51.73	\$116,703
Resubmissions and amendments to registrations	2.50	11,246	28,116	\$51.73	\$1,454,441
<b>Total annual cost savings</b>					<b>\$7,670,835</b>
<b>Costs (costs of proposed regulatory requirements)</b>					
Obtain new NDC number (all regulated products; incremental to self-assignment time)	0.50	11,057	5,528	\$51.73	\$285,984
Submit new listing (All regulated products)	1.00	11,057	11,057	\$51.73	\$571,968
Submit changes to listings (includes withdrawals)	0.50	36,109	18,054	\$51.73	\$933,954
Submit salvage listings	0.17	4,182	697	\$51.73	\$36,055
Submit new registrations	1.00	902	902	\$51.73	\$46,481
Review and update registrations	0.50	9,710	4,855	\$51.73	\$251,139
Expedited updates to registrations	0.25	1,537	384	\$51.73	\$19,875
Certify no change (all new and old) for all listings not changed	0.25	131,072	32,768	\$51.73	\$1,695,089
Obtain user account from FDA	0.25	8,343	1,669	\$51.73	\$86,317
<b>Total yearly cost</b>					<b>\$3,927,062</b>

## **APPENDIX B**

### **EFFECT OF IMPLEMENTATION PERIOD ON LABELING REVISION COSTS**

In order to assess the effect of the length of the implementation period for the NDC number requirements of the proposed rule on the labeling revision costs (see Section 4.2), ERG also calculated labeling revision costs for other implementation periods under consideration. The results are presented in Table B-1 at the end this section.

OTC drug product manufacturers and relabelers and repackagers of OTC drug products are allowed a 7-year implementation period under the proposed rule. In addition to the 7-year implementation period, ERG also considered 5-, 6-, 8-, and 9-year implementation periods for this group. As noted in Section 4.2, ERG estimated in a previous study on pharmaceutical labeling that virtually all OTC drug products have label revisions over any 6-year period. Given that ample space is usually available on OTC drug product labels, the label change required to comply with the proposed rule can likely be accomplished along with regularly scheduled labeling changes. Thus, no costs are estimated for OTC drug products for implementation periods of 6 years or more. However, if firms are only allowed five years to comply with the proposed rule, costs will be incurred for a small number of products that do not revise their labels very frequently. Thus, if FDA selects a 5-year implementation period, ERG estimates that an annualized labeling revision cost of \$2,187,830 will be incurred for 10 percent of OTC drug product SKUs (i.e., 90% will revise labeling along with regularly scheduled label changes).

Prescription drug product manufacturers and relabelers and repackagers of prescription drug products are given 3 years to comply with the requirements of the proposed rule. To investigate the effect of the implementation period on the costs to revise prescription drug product labeling, ERG considered a similar time range for prescription drug

products to that considered for OTC drug products (2 years less and 2 years more than the proposed implementation period). Previously, ERG assumed that with a 3-year implementation period, 75 percent of labels would be revised as part of regularly scheduled label changes (see Section 4.2). These assumptions are modified for the additional implementation periods under consideration and are summarized in Table B-1. If a 1-year implementation period were chosen, labeling revision costs would be \$4.6 million as compared to \$1.2 million cost under a 5-year implementation period. Table B-1 also presents the total annualized cost of the proposed rule (which includes, in addition to the labeling revision cost for prescription drugs for each implementation period considered, the labeling revision costs for OTC drugs, OTC blister packs, and bulk drug substances; intelligence costs from Chapter 3; and costs to acquire software, train for electronic submissions, and submit labeling electronically from Chapter 4).<sup>20</sup> Costs decrease by roughly 1 million for each additional year allowed for implementation.

The incremental cost for revising labeling of OTC drug products with a 5-year implementation period is also presented in the last column of Table B-1, as part of the total annualized costs of the proposed rule for each of the implementation periods under consideration for prescription drug products.

**Table B-1. Impact of a Change in Implementation period on Costs [a]**

<b>Implementation Period for Prescription Drug Products</b>	<b>Prescription SKUs revising labels voluntarily</b>	<b>Annualized Labeling Revision Cost for Prescription</b>	<b>Total Annualized Cost Rule Assuming the Proposed Implementation Period for OTC drugs</b>	<b>Total Annualized Cost of Rule Assuming 5-year Implementation Period for OTC Drugs [c]</b>
1 year	60%	\$4,624,125	\$12,460,740	\$14,648,570
2 years	65%	\$4,046,110	\$11,882,725	\$14,070,554
3 years	75%	\$2,890,078	\$10,726,693	\$12,914,523
4 years	85%	\$1,734,047	\$9,570,662	\$11,758,492

<sup>20</sup> Please note that labeling revision costs for animal OTC and prescription drug products are also included in Table B-1 as part of the prescription drug product costs. ERG only has an estimate of the total number of animal drug SKUs (i.e., not split by OTC/prescription), based on the number of sites that produce animal drugs. ERG's approach is conservative, as it is assumed that costs will be incurred to revise labeling on OTC animal drugs according to the regularly scheduled label changes of prescription drugs.

5 years	90%	\$1,156,031	\$8,992,646	\$11,180,476
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[a] Please note that costs to revise labeling on API products are unaffected by implementation period as they do not have regularly scheduled label changes like OTC and prescription drugs.

[b] These costs assume the proposed implementation period for OTC drug products (7 years), which means no costs are incurred for OTC drug products, as discussed in the text.

[c] These costs include the \$2,187,830 labeling revision cost incurred for OTC drugs if a 5-year implementation period is chosen, as discussed in the text.