DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

Docket No. FDA-2005-N-0464

Final Regulatory Impact Analysis

Final Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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Table of Contents

I. Introduction and Summary 3

A. Introduction 3

B. Summary 4

II. Regulatory Impact Analysis 8

A. Background and Need for Regulation 8

1. Background 8

2. Need for the Rule 10

B. Response to Comments on the Preliminary Impact Analysis of the Proposed Rule 10

C. Who is Affected? 15

D. Benefits of the Final Rule 16

E. Incremental Costs of the Final Rule 17

1. Estimated Impact on Registration and Listing of Drugs and Biological Products Subject to Part 207 18

2. Estimated Impact on Registration and Listing of Human-Blood Products Subject to Part 607 23

3. Estimated Impact on Registration and Listing for Human-Cell and Tissue Products (HCT/P) Subject to Part 1271 24

4. Summary of Total Costs 25

F. Alternatives to the Final Rule 26

1. Certification of No-Changes and Assignment of NDC Numbers 26

2. No New Regulatory Action 27

G. International Effects 27

III. Regulatory Flexibility Analysis 27

A. Small Part-207 Registrants 28

B. Small Part-607 and Part-1271 Registrants 29

IV. References 30

I. Introduction and Summary

A. Introduction

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

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

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for

inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Summary

The final rule clarifies and codifies the Congressionally-mandated requirements in the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) and the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), and adds a few additional requirements to the information needed to list products.

The final rule will affect firms that either register establishments or list products under the following parts of Title 21 of the Code of Federal Regulations.

- Part 207 concerns human drugs, human drugs that are biological products, and animal drugs; throughout this document we use the terms "part-207 products" when referring to drug products and "part-207 registrants" when referring to firms required to register or list under this part.
- Part 607 concerns human blood and blood products; throughout this document we use the terms "part-607 products" when referring to blood and blood products and "part-607 registrants" when referring to firms required to register or list under this part.
- Part 1271 concerns human cells, tissues, and cellular tissue-based products; throughout this document we use the terms "part-1271 products" when referring to these products and "part-1271 registrants" when referring to firms required to register or list under this part.

For part-207 registrants, we estimate the incremental cost of complying with additional

requirements beyond what FDAAA and FDASIA require. Most establishments have submitted registration and listing information electronically since 2009 as required by FDAAA and implemented largely through guidance FDA published in June 2009. Moreover, FDASIA requires domestic and foreign registrants to supply additional information including a unique facility identifier and point of contact email address when registering and listing. Therefore, in the final regulatory impact analysis we do not include the costs and savings of changing from paper submissions to electronic submissions of registration and listing information.

Part-207 registrants required to list will incur incremental costs to: (1) submit either the names and unique facility identifiers (UFIs) of all establishments involved in the production of each unfinished drug received by the registrant for use in the production of the drug being listed or the properly assigned and listed NDC for such unfinished drug; (2) list all inactive ingredients; (3) list legacy products; and (4) certify annually there have been no changes to drugs listings during the previous year. In addition, all affected firms will spend time to read and understand the final rule, and to update standard operating procedures (SOPs).

Part-607 and part-1271 registrants will incur the incremental cost to migrate from paper submissions to electronic submissions. Note that although these registrants are also required to list their products, they will not incur the annual cost of certifying that there are no changes to product listings. However, all these affected firms will spend time to read and understand the final rule, and to update SOPs.

Table 1 summarizes the incremental costs of the final rule. We estimate the one-time costs will equal $59.7 million and annual recurring costs will equal $0.5 million. Over 10 years, the annualized costs equal $9 million when calculated using a 7-percent discount rate or $7.5

million when calculated using a 3-percent discount rate. The largest cost elements will be for registrants to read and understand the rule, and to revise SOPs.

Table 1.—Summary of Total Incremental Cost of the Final Rule ($ millions)

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

Note: Total costs are annualized over a ten-year horizon. Recurring costs include only annual time costs of certifying there are no changes to listings; these costs are unique to part 207. All estimated represent rounded 2014 dollars.

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

Table 1A.—Economic Data: Costs and Benefits Statement

				Units			
Category	Primary Estimate ($millions)	Low Estimate ($millions)	High Estimate ($millions)	Year Dollars	Discount Rate (percent)	Period Covered (years)	Notes

Benefits							
Annualized Monetized $ millions/year							
Annualized Quantified							
Qualitative	The final rule will complete and codify modernization of the registration and listing system, thus allowing FDA to identify establishments, specific drugs or ingredients, to facilitate recalls or information alerts, and to exercise competent oversight of this important industry.						
Costs							
Annualized Monetized $ millions/year	$ 9.0			2014	7	10	Recurring costs include only annual time costs of certifying there are no changes to listings; these costs are unique to part-207 registrants.
	$ 7.5			2014	3	10	
Annualized Quantified							
Qualitative							
Transfers							
Federal Annualized Monetized $ millions/year							
From/To	From:			To:			

Other Annualized Monetized $ millions/year							
From/To	From:			To:			
Effects							
State, Local or Tribal Government: No estimated effect.							
Small Business: The final rule will have little impact on small businesses; annualized costs represent at most, 0.01 percent of annual sales for small firms, and 0.002 percent, for large firms, on average.							

II. Regulatory Impact Analysis

A. Background and Need for Regulation

1. Background

FDA maintains databases that include the identification of establishments involved in the manufacturing; preparation; propagation; compounding or processing of drugs, including the repacking, relabeling, and salvaging of drugs (human and animal prescription and OTC drugs, which includes human biological products, as well as active pharmaceutical ingredients). The databases also identify business operations that take place at each establishment (e.g., manufacturing, repacking, or relabeling), and a list of each drug being manufactured prepared, propagated, compounded, or processed for commercial distribution at each site.

After the proposed rule for establishment registration and drug listing was published in the Federal Register (August 2006; 71 FR 51276), the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) was adopted into law. FDAAA requires the electronic submission of establishment registration and drug listing information unless a waiver is granted. To assist in implementing FDAAA, in June 2009, we announced

publication of a guidance for industry on "Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing", adopting a standardized Structured Product Labeling format with coded data fields (June 1, 2009; 74 FR 26248). FDA began accepting electronic submission of registration and listing information in June 2009. In addition, the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, required facilities to supply additional information including a unique facility identifier and point of contact email address when registering and listing. Based on the foregoing and because establishments have been submitting their registration and listing information electronically for over five years, we are not including the costs and savings of changing from paper submissions to electronic submissions of registration and listing information in the final regulatory impact analysis. Instead, we will estimate the incremental cost of complying with additional requirements beyond current practice of what FDAAA and FDASIA require.

When we estimated the costs for the proposed rule, we did not quantify compliance costs for foreign-based registrants. We determined that the costs to foreign registrants should be included in the impact analysis of the final rule because of the large number of foreign registrants and because all foreign registrants are required to have U.S. agents, who may input the registration and listing information on behalf of their foreign client.

Another significant change from the proposed rule is the assignment of the NDC number. After considering comments, FDA will leave the assignment of the NDC number as current practice, which eliminates the projected costs that third parties such as retail pharmacy chains and prescription benefit managers would have incurred, as well as some costs to the pharmaceutical industry. In this final rule, we clarify the format of the NDC and what changes to existing products will trigger a need for new NDC numbers. However, we do not anticipate a

significant increase in the issuance of NDC numbers because of the changes, or renumbering of currently marketed products.

2. Need for the Rule

The final rule will clarify and codify the existing regulations and procedures concerning establishment registration and drug listing. Without the final rule, some current practices of firms registering establishments and listing products electronically will remain uncodified and may cause confusion about how to make the electronic submission and what information we require that firms submit. Some firms now spend time contacting FDA to clarify what information they need to submit and how to submit it. With more transparency, we expect that firms will avoid unnecessary inquiries. Moreover, without the final rule some information gaps will remain in identifying the source of unfinished drugs, in listing of all inactive ingredients, and an information gap regarding whether some products are still being marketed. Closing these information gaps and codifying electronic registration and listing is necessary so that FDA can exercise uniform, consistent, and timely oversight of part-207, part-607, and part-1271 registrants.

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

Most of the comments on the regulatory impact analysis of the proposed rule (PRIA) concerned the assignment of NDC numbers and the requirement they be printed on container labels. Because these proposed changes are not included in the final rule, the comments are moot and are not discussed here. We also do not discuss the comments on the analysis of the proposed implementation of mandatory electronic registration and listing as this was mandated by statute

as part of FDAAA and has been in place since 2009. Interested parties were able to comment on the burden estimates presented in the guidance, "Providing Regulatory Submissions in Electronic Format--Drug Establishment Registration and Drug Listing" when it was proposed in 2008 (73 FR 39964 - 39968). The remaining comments have been grouped by topic; the order in which they are discussed is not a reflection of importance.

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

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

The PRIA measured the incremental cost to comply with the new or changed requirements on a per-establishment and per-listing basis. Most of the data in the analysis of the proposed rule is not relevant for the final rule because mandatory electronic submission began in

June of 2009 with the statutory implementation authorized by FDAAA; however, the methodology is relevant. We estimated the incremental cost for registration on a per establishment basis. We included all registered establishments in our estimate, so establishments in all industry sectors required to register are included in the analysis if they comply with the requirement. The information required for each establishment is essentially the same. Any economies of scale for a large firm to register multiple establishments at one time are economically insignificant. The same is true for the incremental cost to list products. A contract manufacturer, or a repackager, may have more than one product to list, but the information required for each product is essentially the same for a contract manufacture and other manufacturers. In the final rule, a private label distributer can list the products they distribute on behalf of contract manufacturers but the legal obligation remains the contract manufacturers'.

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

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

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

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

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

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

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

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

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

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

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

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

C. Who is Affected?

The final rule affects part-207 registrants that manufacture or process human and animal drugs and human drugs that are also biological products. Part-207 registrants include manufacturers and processers of human prescription and over-the-counter (OTC) drugs; manufacturers of human biological products; manufacturers of animal drugs; and manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated under section 351 of the Public Health Service Act. The final rule will also affect private label drug distributors who need labeler codes.

The final rule also affects part-607 registrants and part-1271 registrants. Part-607 registrants include manufacturers of blood and blood products. Part-1271 registrants include manufacturers of HCT/Ps that are regulated under section 361 of the Public Health Service Act, but not under

section 351 of the Public Health Service Act. Table 2 describes the number and types of establishments, and the number of listings affected by the final rule.

Table 2.—Number and Type of Establishments Required to Register and List

Affected firms	Total number of establishments	Number of domestic establishments	Number of establishments required to list	Number of listings
Drugs, biologicals (part 207)	9,950	6,450	7,300	136,000
Human-blood (part 607)	2,700	2,509	2,700	2,616
Human-cell and tissue (part 1271)	2,800	2,620	2,800	10,000

Note: some registrants have more than one establishment they register. As a result, there are 5,900 registrants that account for all establishments required to register and list. Part 207 concerns human drugs, human drugs that are biological products, and animal drugs.

D. Benefits of the Final Rule

By codifying the statutory requirements of FDAAA and FDASIA, the final rule clarifies and completes the modernization of our electronic registration and listing systems. Thus, one benefit of the final rule is to improve management of the establishment registration and drug listing requirements and make these processes more efficient and effective for industry and for us. Maintaining a comprehensive electronic registration and listing system supports implementation of the electronic prescribing provisions of the Medicare Prescription Drug Improvement and Modernization Act. Because registrants submit electronic copies of the drug labeling with their drug listings, this rule also ensures the availability of current drug information through DailyMed, a computerized repository of drug labeling maintained by the National Library of Medicine.

Establishment registration information helps FDA identify who is manufacturing, repacking, relabeling, and salvaging drugs and where those operations are performed. Quickly

accessible electronic information about each establishment in the supply chain will help inform our enforcement efforts and improve our oversight of the entire drug supply chain.

Drug listing information also gives FDA a current inventory of drugs manufactured, repacked, relabeled, or salvaged for commercial distribution. Under current practices, registrants would only update listings when the listing information has changed. Consequently, some registrants have never submitted listings in an electronic format. We have identified about 80,000 drugs listed in our legacy system not currently listed in our electronic system. However, we anticipate that registrants no longer market the majority of these drugs. By requiring electronic listings for all marketed drugs, the final rule will modernize our electronic system and close this data gap.

Because the final rule primarily codifies current business practices, we anticipate that most of the benefits of modern electronic registration and listing systems were achieved as firms implemented electronic submissions in response to the FDAAA and FDASIA legislation. The incremental changes required by the final rule will yield benefits in addition to those already achieved. However, we lack sufficient information to quantify these marginal benefits.

E. Incremental Costs of the Final Rule

The final rule will have different incremental costs depending on current practice and on the different burden for part- 207, part-607, and part-1271 registrants. We use an hourly wage of $66.50 from the Bureau of Labor Statistics corresponding to management occupations in pharmaceutical and medicine manufacturing (Ref. 1). We multiply this base wage by a factor of two to adjust for benefits and overhead. The result is an adjusted wage of $133, which we use across all incremental cost categories.

1. Estimated Impact on Registration and Listing of Drugs and Biological Products Subject to Part 207

For part-207 registrants there will not be incremental costs associated with initial, updating, or renewal of registration for establishments when the rule becomes final. The final rule codifies current registration requirements authorized under FDAAA and FDASIA. By contrast, the requirements in §207.49 that will increase the burden for these firms are the identification of source product[1] of the drug being listed, and for some, the submission of all inactive ingredients in the listed drug. However, most incremental costs are one-time costs except for the annually recurring costs of certification of no changes. Table 3 summarizes the estimated costs, and a description of each item follows this table.

Table 3.—Detailed Incremental Costs for Part-207 Registration and Listing ($ millions)

Incremental costs	Frequency	Number of hours per unit	Number of units affected	Cost estimate
Identify source of unfinished drugs (from NDCs)	Once	0.25	93,700 listings	$3.1
Listing inactive ingredients	Once	0.25	40,800 listings	$1.4
Listing legacy products	Once	2.5	26,300 listings	$8.7
Read and understand the final rule	Once	21	5,900 registrants	$16.5
Revise SOPs for all other requirements	Once	19	5,900 registrants	$14.9
Revising SOPs for reusing NDCs	Once	11	2,950 registrants	$4.3
Certification of no-change	recurring annually	0.5	7,300 establishments	$0.5
Total costs (part 207)				**$49.4**

[1] For a finished drug formulation, identification source will be the NDC for the active ingredient; for repackages this will be the NDC number of the finished drug manufacturer.

One-time costs

Registrants will have to submit either the names and unique facility identifiers (UFIs) of all establishments involved in the production of each unfinished drug received by the registrant for use in the production of the drug being listed or the properly assigned and listed NDC for such unfinished drug. If the registrant provides a properly assigned and listed NDC for unfinished drug(s) it uses to produce the listed drug (sometimes referred to as "source NDCs"), the registrant does not need to provide names and UFIs of the upstream establishments. We estimate it will take about 15 minutes (equivalent to 0.25 hours) per listing to gather and enter the information for source NDCs. This requirement applies to 93,700 product listings at most. Using an average wage of $133, the total one-time cost for this requirement is $3.1 million (0.25 hours x 93,700 product listings x $133 wage).

Some registrants may have incremental costs associated with submitting a product's inactive ingredients. We asked for, but did not require, this information on the paper forms and most registrants are submitting inactive ingredients electronically now. However, the list of inactive ingredients may not be complete in all listings. We do not know how many products have incomplete inactive ingredient submissions but believe an upper bound estimate is 25 to 30 percent. With the exception of some OTC-animal drugs, inactive ingredients are listed in the content of labeling, and in all cases the information is readily available. We estimate it will take about 15 minutes to obtain the information from the product label or from other records and enter it into our systems electronically. There are about 136,000 total listings under part 207, and thus 40,800 listings (30 percent) may need to add some, or all, inactive ingredients. We estimate the one-time cost for this requirement is $1.4 million (40,800 listings x 0.25 hours x $133 wage).

Registrants will also incur one-time costs to read and understand the changes to the registration and listing requirements and revise their standard operating procedures (SOPs). We consider that reading and understanding is more complex for firms that are affected the most by the final rule, and so we estimate that it will take 21 hours for each of the 5,900 part-207 registrants to revise their SOPs. We estimate a one-time cost of $16.5 million (5,900 registrants x 21 hours x $133 wage).

All registrants will have to revise their SOPs to describe how to identify and list sources of unfinished drugs, list inactive ingredients, and certify no change to their listings; we assume general registration and listing is already in their SOPs. For registrants with multiple establishments there is an economy of scales in drafting much of the standardized procedures and individualizing them where needed. Based on our experience with such requirements, and also based on a report by the Eastern Research Group (Ref. 2), we estimate SOPs will require 19 hours on average for moderate changes. There are approximately 5,900 registrants affected by these requirements, and using the 19 hour average, we estimate one-time costs of $14.9 million (5,900 registrants x 19 hours x $133 wage) to revise SOPs for all these requirements.[2]

Some registrants will also have to change SOPs regarding the assignment of NDCs. We believe these requirements may impact about 50 percent of registrants. The changes to sections 207.33, 207.35, and 207.37 clarify current policy and most establishments should not need to make any changes to their procedures. Firms that recycled NDC numbers after the original product was off the market for five years will have to make changes to their procedures but they will not have to change existing product-NDC numbers. Some firms may also have to modify

[2] The 5,900 registrants include all registrants whether or not they need to list, but excludes wholesale distributors and third-party logistic providers not required to register.

their procedures regarding what product changes result in the assignment of a new NDC code. We consider this revision to SOPs a small revision, and so we estimate that it will take 11 hours to make this revision; the one-time cost to modify SOPs for the NDC requirements is $ 4.3 million (5,900 registrants x 50 percent x 11 hours x $133 wage). Note that our estimate is an upper bound because firms that will revise their SOPs for identifying sources of unfinished drugs and for listing inactive ingredients will also have to focus their attention on SOP revisions.

The final rule will result in a one-time cost for legacy products. With this rule all product listings will have to be transmitted to FDA electronically to satisfy the listing requirement. When electronic registration and listing became mandatory in 2009, many registrants migrated all of their product listings to the new system, whereas others waited until a product listing needed to be updated before it was submitted electronically. Our legacy database has about 80,000 NDC product codes (submitted on paper forms under part 207 and not yet the subject of an electronic submission); 53 percent are prescription drugs, 42 percent are OTC drugs and the remaining are bulk products. We do not believe that all of these legacy products are still in commercial distribution but those that are will need their listings migrated to our electronic systems within 2 years after the publication of the final rule.

To derive the number of product that will be migrated we eliminated all prescription and bulk drugs from the legacy data, thus only OTC drugs would incur migration costs. For prescription drugs to be reimbursed under Medicare and Medicaid, the NDC number needs to be contained in the National NDC Directory maintained by FDA. The legacy NDCs are not in that directory. Bulk drug manufactures had a greater incentive to migrate their product listings because the NDC is used to identify ingredients in applications and for identifying the active

pharmaceutical ingredient when it is imported and exported; having the product listed electronically helps ensure smoother processing.

To estimate the number of legacy products that will have to list electronically we applied a 4 percent attrition rate over 6 years to the 2008 count of NDCs (80,000). Historically, about 20 to 25 percent of product listings are updated each year and 4 to 6 percent are withdrawn. Thus, we expect there would be 62,621 legacy products in total by 2015. However, only 42 percent of these products would require being entered and updated in our system, this amounts to 26,300 products that will need to be listed electronically.[3] We consider this estimate to be an upper-bound because it is unlikely that so many products would not have needed updates in the past 5 years but it is possible. It will take about 2 hours to enter the currently required information plus an additional one-half hour to comply with the new requirements. The total one-time cost for the electronic listing of the legacy products is $8.7 million (26,300 products x 2.5 hours x $133 wage).

Recurring costs

An annually recurring cost that affects all registrants is the additional costs to certify that there was no change to a listing that was not updated or withdrawn. Section 207.57(b)(2) requires registrants to certify that the listings that were not updated are correct each year when they renew their registration. We estimate that it will take about 30 minutes to verify records and electronically certify per establishment. Based on our registration data there are about 7,300

[3] The 4 percent annual attrition rate means that 96 percent (100 minus 4 percent annual attrition) of NDCs remain for the subsequent year and so forth. Therefore, to calculate the total of legacy products in 2015 based on the count of 2008 (six-year span) we use the formula: 80,000 x (0.96)^6; where 80,000 is the count of legacy products in 2008, 0.96 is the fraction that remains every year, and 6 is the six-year span The result is 62,621, the number of legacy products we expect to have in 2015. Then, we assume only 42 percent of these products are OTCs, so that 26,301 products (62,621 x 0.42) would have to be updated in our system.

establishments with listing obligations. The recurring cost for this requirement is $0.5 million (7,300 establishments x 0.5 hours x $133 wage).

2. Estimated Impact on Registration and Listing of Human-Blood Products Subject to Part 607

The final rule clarifies and codifies current practice for domestic and foreign establishment registration and product listing for human blood and blood products. The final rule will generate one-time costs only but no recurring costs because registrants will not be required to make certification of no changes annually. Table 4 summarizes costs for part-607 registration and listing.

Table 4.—Detailed Incremental Costs for Part-607 Registration and Listing ($ millions)

Incremental costs	Frequency	Number of hours per unit	Number of units	Cost estimate
Read and understand the final rule	Once	14	2,700 registrants	$5.0
Revise SOPs for registration and listing	Once	11	27 registrants	$0.04
Migrating records to FDA's electronic system	Once	1	27 registrants	$0.0
Total costs (part 607)				**$5.1**

Note: the cost estimate shown as $0.0 million represents $3,591 dollars.

One-time costs

All registrants will incur costs to read and understand the final rule; we estimate this will take 14 hours per registrant for a total one-time cost of $5 million (2,700 registrants x 14 hours x $133 wage). We use a 14-hour estimate instead of a 19-hour estimate, as we did for part 207, for reading and understanding because part-607 registrants face fewer requirements.

The only incremental impact on these registrants is that electronic registration and listing is no longer voluntary. There are approximately 2,700 part-607 registrants but only 1 percent, or 27 establishments, will incur costs to comply with this requirement. Based on the estimated annual reporting burden for Form FDA 2838, the paper form used to register and list blood establishments, it will take the registrants about 1 hour to migrate paper records to electronic registration and listing (80 FR 4933). Establishments will also have to make some minor changes to their SOPs, which could require about 11 hours per SOP. Thus, we estimate total one-time cost of $3,591 (27 registrants x 1 hour x $133 wage) plus $39,500 (27 registrants x 11 hour x $133 wage) to go from paper to electronic submission.

3. Estimated Impact on Registration and Listing for Human-Cell and Tissue Products (HCT/P) Subject to Part 1271

The final rule clarifies and codifies registration and listing requirements for establishments that recover, process, store, label, package, or distribute human-cell and tissue products. The final rule also makes electronic submission of registration and listing mandatory. However, the final rule will generate one-time costs only but no recurring costs because these registrants will not be required to make certification of no changes annually.

Table 5.—Detailed Incremental Costs for Part-1271 Registration and Listing ($ millions)

Incremental costs	Frequency	Number of hours per unit	Number of units	Cost estimate
Read and understand the final rule	once	14	2,800 registrants	$5.2
Revise SOPs for registration and listing	once	11	280 registrants	$0.4
Migrating records to FDA's electronic system	once	1	280 registrants	$0.0

Total costs (part 1271)				**$5.7**

Note: the cost estimate shown as $0.0 million represents $37, 240 dollars.

One-time costs

All registrants will incur some additional costs to read and understand the final rule. We estimate that this will require about 14 hours per registrant for a total one-time cost of $5.2 million (2,800 registrants x 14 hours x $133 wage).

Currently, of the 2,800 part-1271 registrants, 90 percent submit registration and listing information electronically already; as a result, only 10 percent of registrants (280 registrants) will incur additional cost for this requirement. Based on the annual reporting burden for Form FDA 3356, it takes about 45 minutes for an initial registration and listing (79 FR 3824); we round this number to one hour for consistency across all parts affected by the rule. Registrants will also need to make minor changes to their SOPs, which could require about 11 hours per registrant. The total one-time incremental cost for the mandatory electronic submission requirement is $37,240 (280 registrants x 1 hour x $133 wage) plus $409,640 (280 registrants x 11 hour x $133 wage) to go from paper to electronic submission.

4. Summary of Total Costs

Table 6 lists the total costs of the rule; this table sums all the different incremental costs from Tables 3, 4, and 5 according to category and frequency. The total cost equal $48.9 million in one-time costs and $0.5 million in annually-recurring costs for part-207 registrants; $5.1 million in one-time costs for part-607 registrants; and $5.7 million in one-time costs for part-1271 registrants. The total annualized costs for all affected parties results in $9 million at a 7-percent discount rate over 10 years or $7.5 million annualized at 3 percent over 10 years.

Table 6.—Summary of Total Incremental Cost of the Final Rule ($ millions)

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

Note: Total costs are annualized over a ten-year horizon. Recurring costs include only annual time costs of certifying there are no changes to listings; these costs are unique to part 207.

F. Alternatives to the Final Rule

1. Certification of No-Changes and Assignment of NDC Numbers

In this final rule we eliminated some of the most burdensome product listing requirements we had proposed in 2006 (71 FR 51276). As discussed in the response to comments, we had proposed to collect batch information and require registrants that did not make changes to a listed product in June or December to certify that the product listing was up-to-date. The requirement of batch information would have increased the number of listings that needed to be updated each June and December. We changed the certification of no change from a product based certification to an establishment based requirement. Certification of accuracy of electronic listings that have not required updates will now be done annually when the establishment renews its registration. With this change the number of certifications decreased from about 100,000 listings to about 10,000 certifications by establishment.

One alternative to the final rule is to require certification of no changes every two years instead of annually. However, the cost of certifying no changes to listings is relatively small, $66.5 dollars per establishment, and the aggregate benefit is an annually-updated system of all listed products.

We also eliminate the proposed change in the assignment of the NDC number. We had proposed that FDA would begin assigning random NDC numbers to new products. Instead we have clarified and codified our current practice.

2. No New Regulatory Action

This alternative is the baseline against which we measure the costs and benefits of the other regulatory alternatives. Under this alternative most registrants would continue to register electronically, but the data gaps in listing all inactive ingredients, listing source NDCs, and certification of no change to legacy products would continue.

G. International Effects

If a foreign establishment distributes an API only outside the United States (i.e., to an establishment that manufacturers finished drugs outside the United States), that foreign establishment is not thereby directly obligated by this final rule to register its establishment and list the API. This is true even if a finished drug containing that API is eventually imported into the United States. However, the establishment that manufactures the finished drug to be imported or offered for import into the United States has an obligation to register and list that finished drug. Based on matching registration and listing records to Dun and Bradstreet data, the majority, 65 percent, of establishments required to register and list are domestic. We also expect that foreign and domestic firms marketing drugs in the US will face the same requirements.

III. Regulatory Flexibility Analysis

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial

number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. Because the costs associated with this rule are expected to be minimal, this final rule would not impose a significant economic impact on a substantial number of small entities. We estimate incremental costs from the final rule will represent 0.01 percent of annual sales for small part-207 registrants and 0.002 percent for large part-207 registrants, on average. The incremental costs are also small for part-607 and part-1271 registrants.

Part-207 registrants are identified by NAICS 325412 for Pharmaceutical-Preparations Manufacturing and NAICS 325414 for Biological-Product Manufacturing. A manufacturer is small if it employs fewer than 750 employees for pharmaceuticals and fewer than 500 employees for biological product manufacturing. Part-607 and part-1271 registrants are identified by NAICS 621991, and according to SBA definitions, an entity in this category is considered small if annual receipts are less than $32.5 million.

A. Small Part-207 Registrants

From the total 9,950 part-207 registrants, there are 6,450 domestic human-drug, animal-drug, and biological-product establishments. Furthermore, 36 percent of these domestic establishments are small. To determine firm size, we match establishments from our electronic registration and listing database to employment and sales data from Dun & Bradstreet (D&B),[4] who classify small businesses according to the SBA guidelines. The impact of the final rule will

[4] Dun & Bradstreet data provide information on both the specific establishment and the parent corporation. Because the costs of compliance would ultimately be reflected on the parent corporation, we use the classification of small firm at the corporate level. In addition, our sample for small firms consists of all parent firms with domestic establishments regardless of location of parent.

vary depending on the number of product listings an establishment has, whether they have previously submitted inactive ingredients, and if and how many legacy products they need to list.

To shed light on the cost per establishment, consider that the upper bound of annualized costs is $7.5 million for part 207 (total costs annualized with a 7-percent discount rate, from Table 1). A simple calculation, dividing this cost by the number of establishments required to list, 7,300, yields an annualized average cost per establishment of $1,021 dollars. We compare this average cost to average annual sales by firm size. Based on Dun & Bradstreet data, average annual sales for small firms range from $8 to $8.2 million; average annual sales for large firms range from $56.8 to $358.7 million.[5] Thus, the annualized costs of the rule represent, at most, 0.01 percent of annual sales for small firms, and 0.002 percent for large firms on average. Our estimates represent average effects, and although some small firms with multiple product listings could incur costs above our average cost estimate, we anticipate that such firms would also have revenues above average sales.

B. Small Part-607 and Part-1271 Registrants

Although most part-607 and part-1271 registrants are small, we anticipate the final rule will not impose significant costs on a significant number of them. The 2007 Census report for Blood and Organ Banks (NAICS 621991) shows that 86 percent of these firms receive below $10 million in annual revenues (Ref. 3). According to SBA definitions for NAICS 621991, an entity in this category is considered small if annual receipts are less than $32.5 million. Thus, it is possible that some of the 14 percent of firms above the $10 million cutoff may be small.

[5] Lower bounds of estimated sales use all domestic observations including observations with zero reported sales, whereas upper bounds use only establishments that have non-zero entries, about half of them.

Therefore, instead of certifying that 86 percent of firms are small, we anticipate that around 90 percent of all part-607 and part-1271 registrants are small entities. However, only 1 percent of part-607 registrants, and 10 percent of part-1271 registrants were still using paper forms to register and list. In addition, the one-time cost per registrant is $1,878 on average ($5.1 million one-time costs divided by 2,700 establishments, from Tables 1 and 2) for part-607 registrants. Similarly, for part-1271 registrants, the one-time cost per registrant is $2,022 on average ($5.7 million one-time costs divided by 2,800 registrants). Lastly, because these registrants do not have to certify if there are no changes to their listings, they will not face recurring costs.

IV. References

1. U.S. Department of Labor, Bureau of Labor Statistics, Occupational Employment Statistics, "May 2013 National Industry-Specific Occupational Employment and Wage Estimates: NAICS 325400 - Pharmaceutical and Medicine Manufacturing," (available at http://www.bls.gov/oes/current/naics4_325400.htm#11-0000).

2. Eastern Research Group, Inc., "Economic Threshold and Regulatory Flexibility Assessment of Proposed Changes to the Current Good Manufacturing Practice Regulations for Manufacturing, Processing, Packing, or Holding Drugs (21 CFR 210 & 211)," pp. 24, 1995.

3. U.S. Census Bureau. American Fact Finder, EC0762SSSZ1, "Health Care and Social Assistance: Subject Series - Estab and Firm Size: Receipts/Revenue Size of Establishments for the United States: 2007 Economic Census of the United States," (available at http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ECN_2007_US_62SSSZ1&prodType=table), 2007.