DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Human Subject Protection; Acceptance of Data From Clinical Investigations for Medical Devices; Final Rule

Docket No. FDA- 2013-N-0080

Final Regulatory Impact Analysis

Final Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 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). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." 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. This final rule is not considered a regulatory action under Executive Order 13771.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small entities are not likely to incur more than one percent of their revenue in costs to comply with the final rule, 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 $148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceed this amount.

The final rule will require that data submitted by sponsors and applicants from clinical investigations conducted outside the United States to support an investigational device exemption (IDE) application, a premarket notification (510(k)) submission, a request for De Novo classification, a premarket approval (PMA) application, a product development protocol (PDP) application, or a humanitarian device exemption (HDE) application be from investigations conducted in accordance with good clinical practice (GCP). We define GCP as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes the review and approval by an independent ethics committee (IEC) before initiating an investigation, continuing IEC review of ongoing investigations, and obtaining and documenting the freely given informed consent of subjects. The changes also require a statement regarding compliance with our regulations for human subject protection, institutional review boards (IRB), and IDEs when the investigations are conducted in the United States. With the above described changes, the rule is intended to update our standards of acceptance of data from clinical investigations and to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects.

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule.

B. Summary

The final rule will require that clinical investigations conducted outside the United States which are used to support IDE applications, 510(k) submissions, De Novo classification requests, PMA applications, PDP applications, or HDE applications conform to GCP. GCP standards include review and approval by an IEC and obtaining and documenting human subjects' informed consent. In addition, the final rule amends the 510(k), HDE, and IDE requirements for our acceptance of data from clinical investigations conducted inside the United States to parallel existing requirements for PMA applications. We have not quantified the benefits of the final rule, which would come from the greater assurance of clinical data quality and integrity, and human subject protection, particularly as it pertains to clinical investigations conducted outside the United States. Costs would arise from increased labor associated with obtaining, documenting and maintaining records to meet the rule's requirements for those that did not already meet the requirements. Total estimated annualized costs of complying with these requirements, over 10 years, range from $0.8 million to $22.1 million with a 7 percent discount rate and range from $0.7 million to $22.0 million with a 3 percent discount rate.

Table 1 summarizes our estimate of the annualized costs and the annualized benefits of the final rule.

Table 1. Summary of Benefits, Costs and Distributional Effects of the Rule ($ millions)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	Qualitative	Increased collection of information that provides greater assurance of clinical data quality and integrity and human subject protection						
Costs	Annualized Monetized $millions/year	$7.4	$0.8	$22.1	2016	7%	10 years	
		$7.3	$0.7	$22.0	2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
		From:			To:			
	Other Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
		From:			To:			
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

Table 2 presents a summary of the Executive Order 13771 impacts of the final rule over an infinite time horizon.

Table 2. EO 13771 Summary Table (in $ millions 2016 dollars, over an infinite time horizon)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	$101.7	$7.9	$311.6	$232.0	$13.0	$721.7
Present Value of Cost Savings	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Present Value of Net Costs	$101.7	$7.9	$311.6	$232.0	$13.0	$721.7
Annualized Costs	$7.1	$0.6	$21.8	$7.0	$0.4	$21.7
Annualized Cost Savings	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Annualized Net Costs	$7.1	$0.6	$21.8	$7.0	$0.4	$21.7

C. Comments on the Preliminary Impact Analysis

We issued a proposed rule on February 25, 2013 to revise the regulations regarding the conditions under which we will accept data from clinical studies in support of IDE applications, 510(k) submissions, PMA applications, PDP applications, and HDE applications. We received numerous comments regarding the proposed rule that were addressed in the preamble. None of the comments addressed the preliminary regulatory impact analysis, provided data about the economic impact or otherwise inferred that the economic analysis should be revised. Despite the lack of comments regarding our regulatory impact analysis, we made some changes in this final regulatory impact analysis. We adjusted our wage rates to 2016 wages. We added the one-time cost for the medical device industry to learn the requirements of the rule. We used the most recent estimate for the number of covered establishments in the medical device industry, and we used a ten-year period of analysis for estimating the present value of the costs.

II. Final Regulatory Impact Analysis

A. Background and Baseline

The current statutory process for marketing a new medical device (which generally includes modified versions of existing products, including those with new or modified indications for use) requires FDA to review applications or submissions that must provide evidence, including data from clinical investigations, of a product's safety and effectiveness or substantial equivalence, as applicable. Table 3A shows the submissions and applications from fiscal years (FY) 2005-2009, which we use as representative for any recent five-year period. IDE applications (including supplements) and 510(k) submissions made up more than 85 percent of the applications (including supplements) and submissions received by FDA's Center for

Devices and Radiological Health (CDRH), followed by PMA and HDE applications (including supplements). Table 3b shows IDE applications (including supplements) and 510(k) submissions, which comprised the majority of the medical device submissions and applications reviewed by FDA's Center for Biologics Evaluation and Research (CBER). We note that CBER did not receive any HDE applications during FY2005 through FY2009.

Table 3A.- Submissions and Applications Received by CDRH in FY 2005-2009

Type of Submission/Application	2005	2006	2007	2008	2009
510(k)	3,650	3,853	3,664	3,849	4,103
HDE					
Original	5	5	6	3	3
Supplements	24	53	24	40	40
IDE					
Original	232	263	225	221	237
Supplements	4,287	4,519	4,378	4,446	4,332
PMA					
Original	48	38	38	31	30
Supplements	796	1,186	1,173	1,551	1,551
Total	9,042	9,917	9,508	10,141	10,296

Note: The number of submissions/applications includes those received by FDA's Office of Device Evaluation (ODE) and Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) (now called Office of In Vitro Diagnostics and Radiological Health, or OIR). Source: FDA Center for Devices and Radiological Health (CDRH).

Table 3B.- Submissions and Applications Received by CBER in FY 2005-2009

Type of Submission/Application	2005	2006	2007	2008	2009
510(k)	63	60	58	53	50
HDE					
Original	0	0	0	0	0
Supplements	0	0	0	0	0
IDE					
Original	8	8	12	7	10
Supplements	227	211	230	323	345
PMA					
Original	5	3	0	0	2
Supplements	14	12	30	33	34
Total	317	294	330	416	441

Source: FDA Center for Biologics Evaluation and Research (CBER).

We include PMA applications in our description of the baseline, but we do not anticipate any economic impact from these applications because current regulations already cover PMAs. Under the existing regulations, data from clinical investigations conducted inside the United States and submitted to support a PMA application may be accepted, provided the clinical investigations are conducted in compliance with the requirements for human subject protection, institutional review boards (IRBs), and IDEs. Moreover, data from clinical investigations conducted outside the United States and submitted to support a PMA application may be accepted provided the investigations are conducted in accordance with ethical principles and the data are valid. Specifically, such clinical investigations must either follow the principles of the 1983 version of the Declaration of Helsinki for human subject protection, or the laws and regulations of the country where the investigation is conducted, whichever accords greater protection to human subjects.

Table 4 provides our estimates of the percent of applications and submissions that use clinical data.[1] The use of clinical data varies by type of application or submission, where the use of clinical data is most prevalent for PMA, HDE and IDE applications.

Table 4.- Use of Clinical Data in Medical Device Submissions/Applications

Type of Submission/Application	CDRH/ODE	CBER

[1] CDRH estimates are based on a sample (n = 342) selected from applications and submissions submitted to CDRH/ODE in fiscal year 2009 which includes all original HDE (n = 3) and PMA (n = 20) applications, and a representative random sample of 510(k) (n = 182) submissions and IDE (n = 137) applications. CDRH estimates do not include applications and submissions to CDRH/OIVD. However, the omission of CDRH/OIVD data is expected to have no more than a minimal effect on the cost estimates because the cost estimates exclude costs associated with PMA applications, only a few HDE applications are received by CDRH each year, and the sample drawn by CDRH/ODE for 510(k) submissions and IDE applications was randomly selected, and is likely representative of the percentage of CDRH/OIVD's 510(k) submissions and IDE applications with clinical data. CBER estimates are based on a sample (n = 339) which includes all original submissions/applications received by CBER during FY2005 through FY2009.

	Pivotal	Any	Pivotal	Any
510(k)	9%	14%	15%	26%
HDE	33%	100%	NA	NA
IDE	28%	64%	20%	78%
PMA	95%	95%	100%	100%

Notes: *Pivotal* includes investigations involving more than 30 human subjects. *Any* includes pivotal, feasibility, safety, and pilot investigations, and investigations with fewer than 30 human subjects. CDRH estimates are based on a sample (n = 342) selected from applications and submissions submitted to CDRH/ODE in fiscal year 2009 which includes all original HDE (n = 3) and PMA (n = 20) applications, and a representative random sample of 510(k) (n = 182) submissions and IDE (n = 137) applications. CDRH estimates do not include applications and submissions to CDRH/OIVD but the omission of CDRH/OIVD data is expected to have no more than a minimal effect on the cost estimates. Total CDRH/ODE sample (n = 342) includes 26 observations where the location of the investigation was unknown. The CDRH/ODE IDE sample includes only active investigations; incomplete, terminated or withdrawn investigations are not included. Total CBER sample (n=339) includes original submissions/applications for FY2005 through FY2009. NA denotes Not Applicable—CBER did not receive HDE applications during FY2005 through FY2009.

For medical devices undergoing premarket approval review, we have always reviewed the safety results of non-IDE clinical investigations conducted outside the United States when submitted. Although clinical investigations conducted outside the United States are not required to be conducted under an IDE, some sponsors consult with FDA and submit a pre-IDE before initiating a foreign clinical investigation. Sponsors also often attempt to develop and implement foreign clinical investigations consistent with United States standards for protocol design and good clinical practice.

Table 5A.- Location of Pivotal Clinical Investigations: CDRH/ODE

Type of Submission/Application	Location of Pivotal Investigations as a Percent of Submissions/Applications in the CDRH/ODE Sample [1]		Location of Pivotal Investigations as a Percent of Submissions/Applications with Pivotal Investigations in the CDRH/ODE Sample	
	US Only	Outside US[2]	US Only	Outside US[2]
510(k)	5%	3%	64%	36%
HDE	0%	33%	0%	100%
IDE	5.6%	16.1%	26%	74%
PMA	65%	30%	68%	32%

Notes: 1. The sample excludes 26 observations where location is unknown. 2. Outside US includes submissions/applications which included investigations conducted either outside the US only or both outside and inside the US. Pivotal clinical investigations involve more than 30 human subjects.

Table 5B.- Location of Pivotal Clinical Investigations: CBER

Type of Submission/Application	Location of Pivotal Investigations as a Percent of Submissions/Applications in the CBER Sample		Location of Pivotal Investigations as a Percent of Submissions/Applications with Pivotal Investigations in the CBER Sample	
	US Only	Outside US[2]	US Only	Outside US[2]
510(k)	15%	0.3%	98%	2%
HDE[1]	NA	NA	NA	NA
IDE	20%	0.0%	100%	0%
PMA	100%	0.0%	100%	0.0%

Notes: 1. Not Applicable--CBER did not receive HDE applications during FY2005 through FY2009. 2. Outside US includes submissions/applications which included investigations conducted either outside the US only or both outside and inside the US. Pivotal clinical investigations involve more than 30 human subjects.

B. Market Failure Requiring Federal Action

An institutional failure exists because the protection of human subjects participating in clinical investigations to support certain medical device applications and submissions can vary depending on the location of the clinical investigation. Standards for the conduct of clinical investigations can also vary by location. To ensure that we receive data that meets our standards for quality and integrity, the final rule will require that data submitted to support applications and submissions come from clinical investigations conducted in accordance with good clinical practice. Moreover, the final rule will correct the institutional failure and ensure that human subjects participating in clinical investigations conducted outside the United States in support of applications and submissions have the same protection, including informed consent, as human subjects participating in clinical investigations conducted in the United States.

C. Benefits of the Rule

Clinical investigations are expensive and demand resource-intensive activities that involve a series of steps that need to be clearly understood and planned to meet regulatory requirements. Requiring that clinical investigations conducted outside the United States comply with GCP should provide greater assurance about the quality and integrity of the resulting data. We are unable to quantify the benefits of the greater assurance for data quality and integrity.

The final rule would further ensure, and require documentation that, the rights and safety of human subjects participating in medical device clinical investigations are protected. That is, requiring explicit documentation of human subject consent, review of clinical investigation conduct by an independent ethics committee (IEC), and reporting of adverse events, decreases the likelihood that human subjects may be placed unnecessarily at risk. Because most foreign clinical investigations are not under FDA review, the final rule would most likely impact human subjects participating in clinical investigations conducted outside the United States. As with the data quality and integrity, we are unable to quantify the benefits of the greater assurance of protection for human subjects.

D. Costs of the Rule

1. Costs – The Time to Learn about the Rule

All medical device manufacturers would incur costs to learn about the requirements of the rule. In 2017, about 17,000 domestic and foreign medical device manufacturers had registered with FDA. To estimate the time to read and understand the rule, HHS guidance (Ref. 1) recommends using reading speeds of 200 words per minute to 250 words per minute. The final rule has approximately 23,000 words. We estimate the time to learn the requirements would be approximately 2 hours (= 23,000 words / 200 words per minute / 60 minutes per hour).

To estimate the cost of a manager's time to read the rule, we use data on the median hourly wage for a General and Operations Manager (occupation code 11-1021) in medical equipment and supplies manufacturing (North American Industry Classification System code 339100). According to the Bureau of Labor Statistics' National Occupational Employment and Wage Estimates, the median wage for this occupation equals $61.20 per hour (Ref. 2). To account for benefits and overhead, we double this value to $122.40 per hour (= $61.20 x 2). We estimate the medical device industry would incur a one-time cost to learn about the rule of about $4 million (= 17,000 manufacturers x 2 hours per manufacturer x $122.40 per hour).

2. The Number of Affected Sponsors

Table 6 presents our estimate for the average number of sponsors submitting clinical data to support 510(k) submissions, HDE applications, and IDE applications to CDRH and CBER for the years 2005 to 2009, which we assume would be typical for estimating annually recurring costs. We assume that every year there will be about the same number of new submissions, so we estimate that the costs will recur annually. As we noted earlier, current regulations already cover clinical data used to support PMA applications, so there would not be additional costs for this type of application. Our analysis assumes that one submission or application represents one sponsor or responder. We determined the range of affected sponsors by taking the primary, minimum and the maximum of the following three estimates:

- Our first estimate is the total number of submissions and applications (original plus supplements, where applicable, from table 3A and table 3B) for the year 2009, times the estimated percent of submissions and applications using pivotal clinical data conducted outside the United States (see the third column in table 5A and in table 5B).

- Our second estimate is the total number of submissions and applications (original plus supplements, where applicable, from table 3A and table 3B) for the year 2009, times the estimated percent of submissions and applications using any type of clinical data (see the third and fifth columns in table 4).
- Our third estimate is based on prior FDA estimates[2] (Refs. 3 -5).

We lack data for De Novo classifications requests that use data from clinical investigations conducted outside the United States. However, we do not believe that excluding this data from our analysis will impact our final cost estimate because we tend to receive fewer requests for De Novo classifications per year than HDE applications (including supplements) and so would be within our estimated ranges. As shown in Table 6, our estimated total number of sponsors potentially affected from the three methods ranges from 632 to 4,721. Our estimate of 632 is the total of the lowest from each of the lowest estimated number of responders (=122+10+500) and our estimate of 4,721 is the total of the highest from each of the highest estimated number of responders (=1,500+43+3,178).

Table 6.- Estimated Number of Responders Affected in a Typical Year (derived from the years 2005 to 2009)

Type of Submission/Application	Estimated Number of Responders Based on				
	Pivotal Clinical Data Outside US	Any Clinical Data	Other FDA Estimate	Low	High
510(k)	122	576	1,500	122	1,500
HDE	14	43	10	10	43
IDE	737	3,178	500	500	3,178

[2] FDA notes that this estimate differs in methodology and sources from the first two estimates.

Total	873	3,798	2,010	632	4,721

Source: Other FDA Estimate from Refs. 3 - 5. Estimated number of responders affected includes submissions and applications received by CBER and CDRH.

3. Estimated Annual Costs of the Final Rule

We estimate a lower and upper bound number of additional labor hours that the final rule would require for recordkeeping and reporting. Our lower-bound is based on estimates derived from FDA experts and reviewers of medical devices (Refs. 3 - 5).

- Additional reporting hours range from 1.25 hours for IDE applications up to 10.75 hours for 510(k) submissions.
- We estimate the additional burden for recordkeeping activities would be one hour per responder.

Our upper-bound is based on estimates for the development of drugs, not medical devices (Ref. 6). The estimate for the recordkeeping and reporting of clinical investigation of drug products ranged from 18 to 32 hours. Based on this, we make an additional assumption that reporting activities could take up to 32 hours and that recordkeeping activities could take up to 18 hours. We also assume that the additional recordkeeping and reporting burden would apply to all submission types (see table 7).

Recordkeeping activities are valued using Office and Administrative Support occupations (SOC 43-0000). The median wage is reported to approximately equal $17.88. To account for benefits and overhead, we double this value to roughly $35.76 (= $17.88 x 2)

As before, the additional labor hours for reporting activities are estimated to be approximately $122.40 per hour adjusted for benefits and overhead. Our estimated cost per responder to comply with the rule are presented in table 7. We use our low and high estimates

for the total cost per responder to estimate the approximate range of the impact per responder in section III, Final Regulatory Flexibility Analysis.

Table 7.- Estimated Additional Labor Hours and Cost per Responder

Type of Submission and Application	Reporting		Recordkeeping		Total Cost per Responder	
	Low	High	Low	High	Low	High
510(k)	10.75	32	1	18	$1,352	$4,560
HDE	8.50	32	1	18	$1,076	$4,560
IDE	1.25	32	1	18	$189	$4,560
Labor Cost (per hour)	$122.40	$122.40	$35.76	$35.76		

Source: Low hours from Refs. 3-5, High hours from Ref. 6.

Using the estimated number of affected sponsors from table 6, and if we assume a low number of responders, we estimate the total annual costs range from approximately $0.3 million to $3 million. When we assume a high number of responders, our estimated annual costs range from $3 million to $22 million. When we assume a midpoint for the number of responders, our estimated annual costs range from $7 million to $12 million. In Table 8a we show that total annual costs range from $0.3 million to $21.6 million.

Table 8a. Estimated Total Annual Costs of the Final Rule ($ million)

	Reporting			Recordkeeping			Total		
Submission or Application Type	Low	Primary	High	Low	Primary	High	Low	Primary	High
510(k)	$0.2	$2.1	$5.9	$0.0	$0.3	$1.0	$0.2	$2.4	$6.9
HDE	$0.0	$0.1	$0.2	$0.0	$0.0	$0.0	$0.0	$0.1	$0.2
IDE	$0.1	$3.7	$12.5	$0.0	$0.6	$2.1	$0.1	$4.4	$14.5
Total	$0.3	$5.9	$18.5	$0.0	$0.9	$3.1	$0.3	$6.9	$21.6

In Table 8b we summarize our estimates of the costs of the final rule discounted over 10 years.

Table 8b. Estimated Summary of Costs of the Final Rule ($ million discounted over 10 years)

	Low	Primary	High
One-time costs	$4.0	$4.0	$4.0
Annual costs	$0.3	$6.9	$21.6
Present Value of Total Costs (7%)	$6.0	$51.8	$155.0
Present Value of Total Costs (3%)	$6.0	$62.2	$187.5
Annualized Costs (7%)	$0.8	$7.4	$22.1
Annualized Costs (3%)	$0.7	$7.3	$22.0

III. Final Regulatory Flexibility Analysis

We have 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 us to analyze regulatory options that would lessen the economic effect of the rule on small entities. This analysis serves as the Final Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

A. Who Would Be Affected

The medical device industry is largely made up of small companies. The Small Business Administration (SBA) uses different definitions of what a small entity is for different industries. Using 2016 SBA size standard definitions, a firm categorized in NAICS codes 339115 (ophthalmic goods manufacturing), 339114 (dental equipment and supplies manufacturing), 339113 (surgical appliance and supplies manufacturing), 339112 (surgical and medical instrument manufacturing), 334517 (irradiation apparatus manufacturing), 334516 (analytical laboratory instrument manufacturing), 334510 (electro medical and electrotherapeutic apparatus), and 325413 (in-vitro diagnostic substance manufacturing) has a threshold range for small from 750 to 1,250 (Ref. 7).

We rely on Dunn & Bradstreet data to estimate the number of establishments by employee size. D&B data indicate that most of the 17,000 establishments in the medical device industry would be considered small (see table 9). As we stated, we estimate that of the 17,000

establishments, there will be approximately 632 to 4,721 respondents per year, which we assume are comparable in size to the overall device industry as measured by the number of employees and sales. Using data at the establishment level further implicitly shows that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

Table 9.- Number of Medical Device Manufacturing Establishments by Employee Size

Number of Employees	Number of Establishments	Percent
0 - 4	9,953	58.55%
5 - 9	2,663	15.66%
10 - 19	1,669	9.81%
20 - 49	1,489	8.76%
50 - 99	576	3.39%
100 - 750	573	3.37%
>750	77	0.45%

B. Estimated Impact on Small Entities

In this section, we determine costs of the final rule as a percent of the average sales for a typical sponsor. Average sales for a typical medical device manufacturer in the employee size groups are shown in table 10. The additional cost of the final rule would represent up to 0.4 percent of sales of a typical manufacturer with fewer than 20 employees (see table 10). The number of establishments that employ fewer than 20 employees represent the majority of the establishments, although establishments with over 750 employees account for over 92 percent of the total average medical device sales. Table 7 shows our estimate for the cost per responder for each type of application or submission which we use for this analysis. To estimate the cost per responder as a percent of sales, we divide the cost per responder by the average sales per establishment.

Table 10. Impact of the Rule to Small Business Entities

Number of Employees	Average Sales	Cost per Responder as a Percent of Sales					
		Low Cost			High Cost		
		510(k)	HDE	IDE	510(k)	HDE	IDE
0-4	$2,095,438	0.072%	0.058%	0.010%	0.243%	0.243%	0.243%
5-9	$1,221,075	0.124%	0.099%	0.017%	0.417%	0.417%	0.417%
10-19	$1,363,636	0.111%	0.089%	0.015%	0.373%	0.373%	0.373%
20-49	$7,065,563	0.021%	0.017%	0.003%	0.072%	0.072%	0.072%
50-99	$7,105,263	0.021%	0.017%	0.003%	0.072%	0.072%	0.072%
100-750	$99,006,623	0.002%	0.001%	0.000%	0.005%	0.005%	0.005%
751-10000	$1,296,296,296	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%

IV. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. Guidelines for Regulatory Impact Analysis, DHHS September 2014, Revised Draft with May 2015 Update

2. Bureau of Labor Statistics. National Occupational Employment and Wage Estimates. Occupational Employment Statistics, May 2016. https://www.bls.gov/oes/current/naics4_339100.htm, accessed June 29 2017.

3. Supporting Statement for Investigational Device Exemptions, OMB No. 0910-0078.

4. Supporting Statement for Premarket Notification, OMB No. 0910-0120.

5. Supporting Statement for Medical Devices; Humanitarian Use Devices, OMB No. 0910-0332.

6. 73 FR 22800, April 28, 2008.

7. Small Business Administration. Table of Small Business Size Standards Matched to North American Industry Classification System Codes. Updated February 26, 2016.-, https://www.sba.gov/contracting/getting-started-contractor/make-sure-you-meet-sba-size-standards/table-small-business-size-standards accessed December 29, 2016.