DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices; Proposed Rule

Docket No. FDA- 2013-N-0080

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Analysis of Economic Impacts

A. Introduction and Summary

1. Introduction

FDA has examined the impacts of the proposed 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 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the requirements are likely to impose a burden on a substantial number of affected small entities, the agency projects that the proposed rule, if finalized, will have a significant economic impact on a substantial number of small entities, and has conducted an Initial Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "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 $136 million, using the most current (2010) Implicit Price

Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

2. Summary

The proposed rule will require that clinical studies conducted outside the United States and used to support investigational device exemption (IDE) applications, premarket notification (510(k)) submissions, premarket approval (PMA) applications, humanitarian device exemption (HDE) applications, or product development protocol (PDP) applications comply with good clinical practice (GCP). GCP standards include review and approval by an independent ethics committee and obtaining and documenting human subjects' informed consent. In addition, the proposed rule seeks to amend the 510(k), HDE and IDE requirements for FDA acceptance of data from clinical studies conducted inside the United States to parallel existing FDA requirements for PMA applications. FDA has not quantified the benefits of the proposed rule which would come from increased collection of information that would provide FDA with greater assurance of clinical data quality and human subject protection, particularly as it pertains to clinical studies conducted outside the United States. Costs would arise from increased labor costs associated with obtaining, documenting and maintaining records to meet the proposed requirements. The estimated costs of complying with these requirements range from $0.30 million to $24.03 million.

B. Need for the Proposed Rule

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 studies, of a product's safety and effectiveness or substantial equivalence, as applicable. As table 1A below indicates, in the fiscal years (FY)

2005-2009, 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). Similarly, IDE applications (including supplements) and 510(k) submissions comprised the majority of the device submissions/applications reviewed by FDA's Center for Biologics Evaluation and Research (CBER) (see table 1B). We note that CBER did not receive any HDE applications during FY2005 through FY2009.

Table 1A.- Submissions/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 Diagnostics (OIVD).
Source: FDA Center for Devices and Radiological Health Research (CDRH).

Table 1B.- Submissions/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).

Under the existing regulation, data from clinical studies conducted inside the United States and submitted to support a PMA application may be accepted provided the clinical studies are conducted in compliance with 21 CFR parts 50, 56, and 812. Moreover, data from clinical studies conducted outside the United States and submitted to support a PMA application may be accepted provided the studies are conducted in accordance with ethical principles and the data are valid. Specifically, such clinical studies 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 study is conducted, whichever accords greater protection to human subjects.

The current regulations do not address FDA's acceptance of clinical data to support 510(k) submissions, and HDE and IDE applications, but in practice, such applications and submissions may be supported by clinical data. Table 2 below provides 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

[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

IDE applications. The medical device industry is witnessing a rapid change in technology and in the adoption of new materials, new modes of action, and new indications which may drive up the volume of clinical trials performed by medical device manufacturers (Ref. 1).

Table 2.- Use of Clinical Data in Medical Device Submissions/Applications

	CDRH/ODE		CBER	
	Clinical Data		Clinical Data	
Type of Submission/Application	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 studies involving more than 30 human subjects. *Any* includes pivotal, feasibility, safety, and pilot studies, and studies 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 study 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, FDA has always reviewed the safety results of non-IDE clinical trials conducted outside the United States when submitted. Although clinical trials conducted outside the United States are not required to be conducted under an IDE, some sponsors consult with FDA, submit a pre-IDE before initiating a foreign trial, and/or often attempt to develop and implement foreign clinical trials consistent with United States standards for protocol design and good clinical practice. However, with the increased number of multinational studies, some of which may not be under FDA purview, and the increased complexity in a study's protocol, it becomes more difficult to ensure human subject

based on a sample (n = 339) which includes all original submissions/applications received by CBER during FY2005 through FY2009.

protection and appropriate clinical study conduct. Examination of the data used in table 2, which contained the location of the clinical studies, indicates that clinical studies are being conducted outside the United States. However, the location of the clinical studies varies by type of submission or application and by center (see table 3A and table 3B).

Table 3A.- Location of Pivotal Clinical Studies: CDRH/ODE

Type of Submission/Application	Location of Pivotal Studies as a Percent of Submissions/Applications in the CDRH/ODE Sample [1]		Location of Pivotal Studies as a Percent of Submissions/Applications with Pivotal Studies 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 studies conducted either outside the US only or both outside and inside the United States. Pivotal clinical studies involve more than 30 human subjects.

Table 3B.- Location of Pivotal Clinical Studies: CBER

Type of Submission/Application		
	Location of Pivotal Studies as a Percent of Submissions/Applications in the CBER Sample	Location of Pivotal Studies as a Percent of Submissions/Applications with Pivotal Studies 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 studies conducted either outside the US only or both outside and inside the United States. Pivotal clinical studies involve more than 30 human subjects.

Several published documents and guidelines on GCP identify principles that provide assurance of the quality and integrity of clinical data and human subject protection. Nonetheless, these documents on their own do not provide FDA assurance of adequate clinical trial conduct and human subject protection since the guidelines do not impose regulatory requirements. While current adoption of the medical device European Directives (Ref. 2) has introduced harmonized requirements for the regulation of medical device studies conducted in Europe, there is ongoing discussion about the variation in the level of enforcement from country to country (Ref. 3).

Thus, without the proposed regulation it is uncertain that sponsors will obtain and maintain documentation to demonstrate compliance with these documents and guidelines. The proposed regulation would require sponsors to provide documentation and maintain records that would provide FDA greater confidence in the quality of data from clinical studies—whether they are conducted inside or outside the United States, and whether they are submitted in support of a PMA, HDE, PDP, 510(k), or IDE—and would further ensure the safety of human subjects.

C. Benefits

Clinical studies are expensive and demand resource-intensive activities that involve a series of steps that need to be clearly understood or planned to meet regulatory requirements. Requiring that clinical studies conducted outside the United States comply with GCP would

improve data quality by providing a standardized approach that includes adverse event reporting, sponsor monitoring, and training of study personnel. FDA is unable to quantify the benefits of data quality improvements; however, receipt of higher quality data may influence the likelihood of approval or provide earlier access to novel medical devices.

Moreover, the proposed rule would further ensure that the rights and safety of human subjects participating in medical device clinical trials are protected. That is, requiring explicit documentation of human subject consent, review of clinical study conduct by an independent ethics committee (IEC), and reporting of adverse events decreases the likelihood that human subjects are placed unnecessarily at risk. Assuming that most foreign clinical trials are not under FDA review, the proposed rule would most likely impact human subjects participating in clinical trials conducted outside the United States. A recent study (Ref. 4) estimated that over 200,000 foreign subjects were involved in clinical studies that supported marketing applications submitted to FDA's Center for Drug and Evaluation Research (CDER) in 2008. Examination of a database, clinicaltrials.gov, suggests that the number of patients enrolled could be substantial. Even assuming that foreign clinical studies involving medical devices would involve 10 percent of the 200,000 subjects involved in foreign clinical studies related to drugs, the proposed rule would impact at least 20,000 human subjects. Thus, the benefits of the proposed rule would impact a substantial number of human subjects participating in clinical studies involving medical devices.

D. Costs of the Proposed Rule

1. The Number of Affected Sponsors

Table 4 presents the estimated number of sponsors submitting clinical data to support 510(k) submissions, and HDE and IDE applications to CDRH and CBER. Since current regulations already cover clinical data used to support PMA applications, no additional costs are anticipated for this type of application. This analysis assumes that one submission or application

represents one sponsor or responder. The range of affected sponsors is determined by taking the minimum and maximum of the following three estimates. The first estimate is based on the total number of fiscal year 2009 submissions and applications (original plus supplements, where applicable, from table 1A and table 1B) times the estimated percent of submissions and applications using pivotal clinical data conducted outside the United States (see the third column in table 3A and in table 3B). The second estimate is based on the total number of fiscal year 2009 submissions and applications (original plus supplements, where applicable, from table 1A and table 1B) times the estimated percent of submissions and applications using any type of clinical data (see the third and fifth columns in table 2). The third estimate is based on prior FDA estimates[2] (Refs. 5-7). The estimated number of sponsors affected ranges from 632 to 4,721 (see table 4).

Table 4.- Estimated Number of Responders Affected

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

Source: Other FDA Estimate from Refs. 5-7. Estimated number of responders affected include submissions/applications received by CBER and CDRH.

2. Estimated Costs of the Proposed Rule

The estimated additional number of labor hours that the proposed rule would require is determined as follows. The lower-bound is based on estimates derived from FDA experts and reviewers of medical devices (Refs. 5-7). The estimated additional reporting hours range from 1.25 hours for IDE applications and up to 10.75 hours for 510(k) submissions. The additional burden for recordkeeping activities is estimated at 1 hour per responder.

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

The development process for drugs generally involves more clinical studies than the development process for medical devices. Thus, the upper-bound is based on estimates related to drug development (Ref. 8). Since the prior estimate for drug products, which ranged from 18 to 32 hours, included both recordkeeping and reporting activities, we make additional assumptions. Specifically, we assume 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 burden is uniform across submission types (see table 5). FDA welcomes comments on the estimated range of additional labor hours described above.

The additional labor hours are valued using median hourly wages in the pharmaceutical and medical manufacturing industry (North American Industry Classification, NAICS, code 325400) as reported by the Bureau of Labor Statistics May 2010 National Occupational Employment and Wage Estimates (Ref. 9). Specifically, reporting activities by regulatory affairs managers are valued using median hourly wages for Natural Sciences Manager occupations (Standard Occupational Classification, SOC, 11-9121) and recordkeeping activities are valued using Office and Administrative Support occupations (SOC 43-0000). The wages are adjusted for benefits and overhead. The estimated additional cost per responder ranges from $210 to $5,093 (see table 5).

Using the estimated number of affected sponsors from table 4, the estimated total annual costs range from $0.30 million to $3.22 million assuming a low number of responders. On the other hand, estimated costs range from $2.99 million to $24.04 million assuming a high number of responders (see table 6).

Table 5.- Estimated Additional Labor Hours and Cost per Responder

Type of Submission/Application	Reporting		Recordkeeping		Total Cost per Responder	
	Low	High	Low	High	Low	High

510(k)	10.75	32	1	18	$1,518	$5,093
HDE	8.50	32	1	18	$1,208	$5,093
IDE	1.25	32	1	18	$210	$5,093
Labor Cost (per hour)	$137.62	$137.62	$38.26	$38.26		

Source: Low hours from Refs. 5-7, High hours from Ref. 8.

Table 6.- Estimated Total Cost of the Proposed Rule

Type of Submission/ Application	Reporting		Recordkeeping		Total	
	Low	High	Low	High	Low	High
Low Number of Responders						
510(k)	$179,809	$535,245	$4,650	$83,703	$184,459	$618,948
HDE	$11,698	$44,038	$383	$6,887	$12,080	$50,925
IDE	$86,013	$2,201,920	$19,130	$344,340	$105,143	$2,546,260
Total	$277,519	$2,781,203	$24,163	$434,929	$301,682	$3,216,133
High Number of Responders						
510(k)	$2,219,123	$6,605,760	$57,390	$1,033,020	$2,276,513	$7,638,780
HDE	$50,300	$189,365	$1,645	$29,613	$51,945	$218,978
IDE	$546,761	$13,997,085	$121,605	$2,188,888	$668,366	$16,185,973
Total	$2,816,184	$20,792,210	$180,640	$3,251,521	$2,996,824	$24,043,731

E. Sensitivity Analysis

In this section we estimate costs assuming different rates of foreign clinical data submission. Table 7A presents the number of responders based on rates from 10 percent to 100 percent. FDA notes that under this scenario, it is assumed that all submissions and applications include data from studies outside of the United States at a uniform rate. Thus, at a low rate of clinical data use, the number of responders would be lower than the estimates of the proposed rule.

Table 7A.- Number of Responders Affected Under Various Assumptions

Percent of Responders Using Clinical Data	Number of Responders by Type of Submission/Application				Change from the Baseline	
	510(k)	IDE	HDE	Total	Low	High
10%	415	492	4	912	280	(3,809)
25%	1,038	1,231	11	2,280	1,648	(2,441)

50%	2,077	2,462	22	4,560	3,928	(161)
75%	3,115	3,693	32	6,840	6,208	2,119
90%	3,738	4,432	39	8,208	7,576	3,487
100%	4,153	4,924	43	9,120	8,488	4,399

Note: Numbers in parentheses denote a decrease from the estimates in table 4. Change from the Baseline denotes a comparison with low and high responders.

The estimated total costs when per responder costs are "Low" and "High" are presented in table 7B and table 7C, respectively, under the assumption of Low and High number of responders. Assuming that every submission or application would include clinical data the estimated cost is $7.39 million when reporting and recordkeeping costs are low (see table 7B). Meanwhile, when costs per responder are high, the estimated total costs go up to $46.44 million (see table 7C).

Table 7B.- Sensitivity Analysis Assuming Low Cost

Percent of Responders Using Clinical Data	Low Cost				Change from the Baseline	
	510(k)	IDE	HDE	Total	Low	High
10%	$630,290	$103,544	$5,195	$739,029	$437,347	($2,257,795)
25%	$1,575,726	$258,861	$12,986	$1,847,573	$1,545,891	($1,149,251)
50%	$3,151,452	$517,722	$25,973	$3,695,146	$3,393,465	$698,323
75%	$4,727,178	$776,583	$38,959	$5,542,720	$5,241,038	$2,545,896
90%	$5,672,614	$931,899	$46,751	$6,651,264	$6,349,582	$3,654,440
100%	$6,302,904	$1,035,443	$51,945	$7,390,293	$7,088,611	$4,393,469

Note: Numbers in parentheses denote a decrease from the cost estimates in table 6. Change from the Baseline denotes a comparison of the costs for low or high responders.

Table 7C.- Sensitivity Analysis Assuming High Cost

Percent of Responders Using Clinical Data	High Cost				Change from the Baseline	
	510(k)	IDE	HDE	Total	Low	High
10%	$2,114,924	$2,507,557	$21,898	$4,644,378	$1,428,245	($19,399,353)
25%	$5,287,309	$6,268,892	$54,745	$11,610,946	$8,394,813	($12,432,785)
50%	$10,574,618	$12,537,784	$109,489	$23,221,891	$20,005,758	($821,840)

75%	$15,861,927	$18,806,676	$164,234	$34,832,837	$31,616,704	$10,789,106
90%	$19,034,312	$22,568,012	$197,081	$41,799,404	$38,583,271	$17,755,673
100%	$21,149,236	$25,075,568	$218,978	$46,443,782	$43,227,650	$22,400,051

Note: Numbers in parentheses denote a decrease from the cost estimates in table 6. Change from the Baseline denotes a comparison of the costs for low or high responders.

F. Analysis of Regulatory Alternatives

The proposed rule would require additional maintenance, retention, and submission of documents indicating (1) clinical studies conducted outside the United States and used to support IDE or device marketing applications or submissions are conducted in accordance with GCP, and (2) availability of data for FDA inspection, if deemed necessary. FDA identified the following alternatives: (1) no regulation, (2) publish a guidance document only, and (3) increase FDA oversight of foreign clinical studies.

Alternative 1: No Change in Regulation

A simple alternative (and the baseline for this analysis) would be to leave the current regulation unchanged. While this alternative would not impose additional costs on sponsors of clinical studies that may be used to support IDE or marketing applications or submissions for medical device products, the standards for protecting humans subjects and ensuring the quality and integrity of data would not be updated and the benefits of this option would be uncertain.

Alternative 2: Publish Guidance

While several documents have been published to provide guidance on GCP, guidance alone cannot impose new regulatory requirements. Without regulation that makes all parties to a study responsible, human subject protection and the appropriate conduct of clinical studies would be uncertain.

Alternative 3. Increase FDA Oversight of Foreign Clinical Trials

FDA has identified increasing the number of foreign inspections as an alternative to the proposed rule. The average cost of a foreign medical device inspection to FDA is $31,100 plus overhead. Assuming 48 percent in overhead costs, the additional cost per medical device

inspection would be $46,028. Thus, the difference in per responder cost between the proposed rule and Alternative 3 would be between $40,935 ($46,028 minus $5,093) and $45,818 ($46,028 minus $210).

Inspections are resource-intensive activities, thus FDA is unable to inspect all of the facilities in any one year; an earlier study conducted for drug products reports that only 0.7 percent of FDA clinical trial inspections are foreign inspections (Ref. 4). Using the range of low and high responders reported in table 4 as the baseline for the number of clinical trials that may be inspected, FDA estimates that the total cost of inspecting up to 15 percent of clinical trials (15 percent of 4,721 is 708) could be up to $32,597,364 (708 times $46,028). Table 8 presents the estimated costs of inspecting 0.7, 5, 10 or 15 percent of responders who conduct clinical studies. The additional inspection cost is estimated by taking the difference in cost between the baseline number of inspections at 0.7 percent and the alternative. For example, for the Low Responder inspections, $1,521,210 minus $203,480 would result in an estimated additional cost of $1,249,948 to increase inspections from 0.7 percent to 5 percent.

Table 8.- Estimated Foreign Inspection Costs

Percent Inspected	0.7%	5%	10%	15%
Low Responders	4	32	63	95
High Responders	33	236	472	708
Cost per Foreign Inspection	$46,028	$46,028	$46,028	$46,028
Total Estimated Inspection Cost				
Low Responders	$203,480	$1,453,427	$2,906,855	$4,360,282
High Responders	$1,521,210	$10,865,788	$21,731,576	$32,597,364

Comparing the costs of Alternative 3 and the proposed rule, we find that increasing the number of inspection from the existing 0.7 percent up to 5 percent may result in savings relative to the proposed rule (see table 9). However, increasing the number of foreign inspections would limit inspections to the sample of clinical studies under FDA oversight, and would not ensure

GCP compliance and human subject protection in all other clinical trials. Furthermore, as table 8 shows, costs rise in the number of inspections, so that inspecting up to 15 percent of the clinical trials can lead to costs exceeding those of the proposed rule.

Table 9.- Difference in Cost Between Alternative 3 and the Proposed Rule

		Increase Foreign Inspections		
Total Cost	Proposed Rule	up to 5%	up to 10%	up to 15%
Low Responders				
Low	$301,682	$948,266	$2,401,693	$3,855,120
High	$3,216,133	($1,966,185)	($512,758)	$940,670
High Responders				
Low	$2,996,824	$6,347,754	$17,213,542	$28,079,330
High	$24,043,731	($14,699,153)	($3,833,365)	$7,032,423

Note: Savings are denoted in parentheses.

II. Regulatory Flexibility Analysis

FDA has examined the economic implications of the proposed 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. This analysis serves as the Initial 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 2009 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), 335410 (electromedical and electrotherapeutic apparatus),

and 325413 (in-vitro diagnostic substance manufacturing) is considered small if it employs 500 or fewer people (Ref. 10).

Dunn & Bradstreet (Dunn & Bradstreet, Inc.) data on the number of establishments by employee size for the year 2009 indicate that most of the 17,932 establishments have employee sizes by which they would be considered small (see table 10). Using data at the establishment level implicitly assumes that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

Table 10.- Number of Medical Device Manufacturing Establishments by Employee Size

Number of Employees	Number of Establishments	Percent
0 - 4	10,499	58.55%
5 - 9	2,809	15.66%
10 - 19	1,760	9.81%
20 - 49	1,571	8.76%
50 - 99	608	3.39%
100 - 500	604	3.37%
501 - 10,000	81	0.45%

B. Estimated Impact to Small Entities

In this section, we determine costs of the proposed 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 11. The additional cost of the proposed rule would represent up to 0.4 percent of sales of a typical manufacturer with fewer than 20 employees (see table 11). While the number of establishments that employ fewer than 20 employees represents the majority of the establishments, establishments with over 500 employees account for almost 92 percent of the total average medical device sales. By comparison, in 2004, it was reported that firms with over 500 employees sold 90 percent of medical device sales (Ref. 11). The agency

tentatively concludes that the proposed rule would have a significant impact on a substantial number of small entities, but the impact is uncertain.

Table 11.- 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%
100-500	$99,006,623	0.002%	0.001%	0.000%	0.005%	0.005%	0.005%
501-10000	$1,296,296,296	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%

C. An Alternative to the Proposed Rule

An alternative that would provide regulatory relief would be to exempt small entities. Exempting small entities from the proposed requirements would result in an estimated annual savings of up to 0.4 percent of average sales for small-sized firms. However, the proposed requirements assure FDA that clinical trial participants are not exposed to unnecessary risks and that all clinical investigations are conducted according to good clinical practice.

D. Outreach

We are publishing this proposed rule in anticipation of receiving comments from affected small entities. The proposed rule is available to all interested parties through FDA's Internet Web site at

http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

III. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not

responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1.1. Wright, D. 2002. Medical Devices on Trial, Part I. *Medical Device Technology,* 13(10): (35-38). Available from: Business Source Complete, Ipswich, MA, accessed April 2011.

1.2. Medicines and Healthcare Products Regulatory Agency. Medical Devices Directive. http://www.mhra.gov.uk/Howweregulate/Devices/MedicalDevicesDirective/index.htm, accessed May 2011.

1.3. Donawa, M. 2007. Risk Management of European Device Clinical Studies. *Medical Device Technology,* 18(2): 39-42. Available from: Business Source Complete, Ipswich, MA, accessed May 2011.

1.4. Levinson, D.R. Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials, Department of Health and Human Services, Office of Inspector General, OEI-01-08-00510, June 2010., http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf, accessed April 2011.

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

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

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

1.8. 73 FR 22800, April 28, 2008.

1.9. Bureau of Labor Statistics. National Occupational Employment and Wage Estimates. Occupational Employment Statistics, May 2010. http://www.bls.gov/oes/current/oes_nat.htm, accessed May 2011.

1.10. Small Business Administration. Table of Small Business Size Standards Matched to North American Industry Classification System Codes. November 2010. http://www.sba.gov/sites/default/files/Size_Standards_Table.pdf, accessed April 2011.

1.11. Anderson, C. 2008. Trends in FDA CDRH Bioresearch Monitoring Inspections. *Journal of Clinical Research Best Practices¸4(7): 1-6.* http://firstclinical.com/journal/2008/0807_CDRH_Monitoring.pdf, accessed March 2011.