DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Investigational New Drug Application Annual Reporting

Docket No. FDA-2020-N-0258

Preliminary Regulatory Impact Analysis
Initial 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 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 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). The Office of Information and Regulatory Affairs has determined that this proposed rule is an economically 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 proposed requirements are unlikely to impose a substantial burden on the affected small entities, we propose to certify that the proposed rule is unlikely to 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 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 $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The proposed rule seeks to revise FDA's regulations for investigational new drug application (IND) annual reporting. The proposed rule would modify the format and content of the IND annual report to be generally consistent with those of the development safety update report (DSUR) standards devised by the International Council for Harmonisation of Technical Requirements for Human Use (ICH), which is described in FDA's guidance for industry entitled "E2F Development Safety Update Report" (E2F DSUR). The proposed harmonization would result in savings in labor costs for sponsors who may no longer have to prepare a different type of periodic safety report for submission to certain other countries or regions in which a drug might be studied. Moreover, FDA would receive safety data on investigational new drugs that is more comprehensive, which would enhance our ability to oversee the progress and safety of clinical investigations. The estimate of annualized benefits over 10 years ranges from $47.86 million to $117.99 million with a primary value of $86.46 million at a 7 percent discount rate and from $49.24 million to $121.01 million with a primary value of $88.79 million at a 3 percent discount rate. The primary estimate of the present value of benefits over 10 years is $607.29 million at a 7 percent discount rate and $757.38 million at a 3 percent discount rate.

Costs to industry would arise from increased labor associated with preparing and submitting a periodic safety report that is more comprehensive to meet the proposed requirements. Costs to government would arise from increased FDA resources being used to review the more comprehensive report. The estimate of annualized costs over 10 years ranges from $40.43 million to $101.34 million at a 7 percent discount rate with a primary

value of $61.11 million. Using a 3 percent discount rate, the annualized costs range from $40.89 million to $102.48 million with a primary value of $61.81 million. The primary estimate of the present value of costs over 10 years is $429.20 million at a 7 percent discount rate and $527.21 million at a 3 percent discount rate.

Table 1. Summary of Benefits and Costs in Millions of 2020 Dollars Over a 10 Year Time Horizon

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $/year	$86.46	$47.86	$117.99	2020	7%	10 years	Benefits are estimates in terms of cost savings.
		$88.79	$49.24	$121.01	2020	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $/year	$61.11	$40.43	$101.34	2020	7%	10 years	
		$61.81	$40.89	$102.48	2020	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: None Small Business: Annual costs per affected small entity represent a maximum of 0.61 percent of average receipts. Wages: None Growth: None							

II. Preliminary Regulatory Impact Analysis

A. Background

The IND regulations in part 312 (21 CFR part 312) contain procedures and requirements governing the use of investigational drugs, including biological products that do not also meet the definition of *device* under the Federal Food, Drug, and Cosmetic Act,[1] and contain procedures and requirements for the submission of INDs to FDA and for FDA's review of those INDs. The IND regulations provide various mechanisms for continued FDA oversight of clinical investigations conducted under an IND. FDA regulations currently require sponsors to submit a brief report of the progress of investigations in an annual report (§ 312.33). The IND annual report currently required under § 312.33 is intended to serve as the means for reporting the status of studies being conducted under the IND and for providing the general investigational plan and safety-related changes to the investigational plan for the coming year.

Because of the increasing complexity of clinical studies, having periodic reporting and consistent information reported are of increased importance for protecting human subjects from unnecessary risks. The increasing size and scope of trials underpin the need for information and analyses that are more comprehensive to further assist FDA in evaluating the evolving safety and efficacy profile of a drug during development and, in particular, identifying safety signals during the conduct of clinical trials. Additionally,

[1] *See* 21 U.S.C. 201(g)-(h), 42 U.S.C. 262(i)-(j); *see also* 21 C.F.R. 601.21.

there have been concerns about differences in the content and objectives between the current IND annual report and the annual safety report that is being used in other countries, as well as concerns about the burden associated with preparing different periodic safety reports for different regulatory authorities. These concerns led to an international effort to develop a common periodic safety report that could be used globally to satisfy reporting requirements. In June 2008, the draft International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for the E2F DSUR was approved by the ICH steering committee (Ref. 6). In the *Federal Register* of August 5, 2008 (73 FR 45462), FDA announced the availability of the draft guidance for industry entitled "E2F Development Safety Update Report" for public comment, which was the guideline prepared with the support and approval of the ICH (Ref. 7). After consideration of the comments received on the draft guidance for industry, the ICH steering committee approved a final draft of the guideline to be adopted by the United States, Japan, and participating European countries entitled "Development Safety Update Report, E2F," dated August 17, 2010 (Ref. 6). In the *Federal Register* of August 23, 2011 (76 FR 52667)), FDA issued this guideline as a final guidance for industry entitled "E2F Development Safety Update Report." This guidance discusses the format, content, and timing of submission of a DSUR as developed by the ICH (referred to as the E2F DSUR in this document) (Ref. 1).

The proposed FDA DSUR is intended to be consistent with the format and content of the E2F DSUR supported by ICH for annual reporting in certain other countries and regions.

B. Need for Federal Regulatory Action

The current IND annual report differs from the E2F DSUR in: (1) the filing date and (2) the format and content (Refs. 2 and 3).[2] Another difference is that the E2F DSUR recommends inclusion of detailed information on safety for individual clinical trials. These differences can lead to inconsistent information being provided to regulatory Agencies and inefficiencies such as higher preparation costs. The greater harmonization of the format, content, and timing of the submission of annual safety reports will help ensure that annual safety reports are of high quality and are uniform and comprehensive (Ref. 3).

The proposed rule would replace the existing IND annual report with an annual safety report that is generally consistent with the format and content of the DSUR devised by the ICH and described in the E2F. The proposed FDA DSUR would reflect the current state of drug development, and it would be generally consistent with internationally recommended standards. The proposed changes would require submission of more comprehensive data analyses and safety information that are important for the ongoing assessment of the safety of the drug under development. The new information would further enhance the means by which FDA can (1) monitor the quality and progress of an investigation, (2) assess the safety and efficacy of a potential new drug, and (3) ensure the protection of human subjects. Besides greater

[2] In June 2008, the International Conference on Harmonisation issued a draft guidance (73 FR 45462 at 45463) that described the format, content, and timing of the submission of the DSUR for an investigational drug. The objective of the DSUR is to present an annual review and evaluation of safety information on an investigational drug, which would be standard among the EU, Japan, and the United States (at that time, the ICH regions). As of June 11, 2011, the EU Clinical Directive 2001/20EC incorporated the format and content of the ICH DSUR

harmonization of regulatory requirements and enhancing FDA's ability to oversee the conduct of clinical trials and the safety of human subjects, the proposed rule could potentially lead to more efficient use of resources.

C. Purpose of the Proposed Rule

FDA is proposing to replace the current annual report with a new report entitled "Development Safety Update Report" that is generally consistent with the format and content of the DSUR devised by the ICH. FDA is proposing this action because of the advantages that the proposed FDA DSUR would provide over the current IND annual report in helping to protect the public health, including helping to ensure subject safety, providing more useful, comprehensive information, and creating some of the efficiencies associated with a report that is more similar to those required by multiple regulatory authorities.

D. Baseline Conditions

The effects of the proposed rule are estimated relative to a baseline. The baseline represents the state of the world in the absence of the proposed regulatory action. In our analysis, we describe baseline conditions in terms of the number of annual safety reports submitted and clinical trials conducted. We assume that preparing an IND annual report that meets the current regulatory requirements would take 360 hours and that these labor hours are allocated among clerical (25 percent), statistical (25 percent), and regulatory affairs activities (50 percent) (76 FR 4914 at 4916 and 75 FR 59935 at 59958). That is, to prepare the current IND annual report, the estimated number of hours among clerical, statistical, and regulatory affairs activities are, respectively, 90 (360 x 0.25), 90 (360 x 0.25), and 180 (360 x 0.50).

To estimate the baseline costs to prepare the current IND annual report we use 2020 median wages plus benefits and other indirect costs as reported by the U.S. Department of Labor's Bureau of Labor Statistics (Ref. 11) for Pharmaceutical and Medicine Manufacturing (North American Industry Classification System (NAICS) code 325400).[3] The hourly labor costs equal $44.54 for clerical staff, $100.32 for statisticians, and $134.30 for regulatory affairs managers. Thus, the current baseline costs for an IND annual report total about $37,211 (= ($44.54 per hour x 90 hours) + ($100.32 per hour x 90 hours) + ($134.30 per hour x 180 hours)).

Current regulations for IND annual reporting were finalized at a time when clinical investigations were generally smaller than current trials and did not often include foreign sites (Ref. 5). However, since the regulations for IND annual reporting were finalized, clinical studies have grown in size and complexity and have grown in the number of procedures per patient and the number of countries involved (Refs. 6 through 9).

Table 2 demonstrates an increasing trend in the number of IND annual reports submitted to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). There were 8,664 total annual reports submitted in 2010. The total number of annual reports submitted to FDA has increased by 53 percent since 2010. In 2020, there were 11,091 annual reports submitted to CDER and 2,207 reports submitted to CBER, for a total of 13,298 reports.

[3] We multiple wages by 2 to account or benefits and other indirect costs (Ref. 20).

Table 2. Annual Reports received by FDA for 2010–2020

Year	Annual Reports		
	CDER	CBER	Total
2010	7,826	1,258	8,664
2011	8,220	1,508	9,728
2012	7,892	1,470	9,362
2013	8,138	1,593	9,731
2014	8,545	1,618	10,163
2015	9,027	1,688	10,715
2016	9,397	1,789	11,186
2017	9,891	1,856	11,747
2018	10,470	2,043	12,513
2019	10,992	2,174	13,166
2020	11,091	2,207	13,298

Source: Internal FDA data gov as of August 2021.

This analysis assumes that the increasing trend in IND annual reports experienced between 2010 and 2020 continues into the future. The number of IND annual reports received over the period of 2010 to 2020 experienced an average annual growth of approximately 4.4 percent (see Table 2). Table 3 displays the counts of annual reports that would be received under the assumption that the 4.4 percent growth rate continues between 2021 and 2030. By 2030, FDA would receive a total of 20,455 IND annual reports.

Table 3. Expected Annual Reports for Drug and Biologic Products for 2021–2030 with a 4.4 Percent Growth Rate

Year	Annual Reports		
	CDER	CBER	Total
2021	11,579	2,304	13,883
2022	12,088	2,405	14,494
2023	12,620	2,511	15,132
2024	13,176	2,622	15,797
2025	13,755	2,737	16,493
2026	14,361	2,858	17,218
2027	14,993	2,983	17,976
2028	15,652	3,115	18,767
2029	16,341	3,252	19,593
2030	17,060	3,395	20,455

E. Benefits of the Proposed Rule

We estimate the quantifiable benefits of this proposed rule as the cost savings brought about by harmonization resulting from a reduction in labor hours needed by certain sponsors to prepare and submit periodic safety reports to varying regulatory authorities. FDA began accepting voluntary DSUR submissions in place of the IND annual report following the 2011 final guidance (76 FR 52667). FDA estimates the quantifiable benefits by determining the number of labor hours that it would take to produce the proposed FDA DSUR and by determining the number of sponsors who currently submit more than one periodic safety report less any sponsors voluntarily submitting the annual report in DSUR format.

Under the proposed requirements of the rule, FDA would receive information that is more comprehensive, such as the requirement for an integrated overall safety analysis and a summary of cumulative pertinent safety information. Receiving information that is more comprehensive would further enhance FDA's ability to monitor the quality and progress of an investigation. However, because we are unable to measure the value of this information, FDA is unable to quantify the expected benefits that would come from receiving reports that are more comprehensive and informative, that would strengthen FDA's ability to assess the safety and efficacy of investigational drugs, and would further help protect participants of clinical investigations.

FDA assumes the beneficiaries of harmonization are sponsors that have an IND with FDA and conduct clinical trials in a member or observer country of the ICH.[4] This analysis assumes that all ICH countries require submission in DSUR format. Any study with an IND with FDA must submit an annual report to FDA under § 312.33. We assume that sponsors conducting a clinical trial in a country outside of US are submitting a safety report to that country's respective regulatory authority. For trials located in countries under the European Medicines Agency's jurisdiction, we assume the sponsor is submitting one report to the EMA that covers all EMA countries that the study is located in.[5]

[4] Refer to https://www.ich.org/page/members-observers for a comprehensive list of ICH countries.
[5] Under the Clinical Trials Directive, sponsors are currently required to submit a copy of the DSUR to national competent authorities of the EU Member States / European Economic Area (EEA) countries and ethics committees via national processes (see https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/reporting-safety-information-clinical-trials). With full implementation of the Clinical Trial Regulation, sponsors will be able to submit the DSUR *centrally* to the Clinical Trials Information System (CTIS). Until January 31, 2023, clinical trial sponsors can choose whether to apply to start a clinical trial via the CTIS or under the Clinical Trials Directive.

We use data collected by the National Institutes of Health (NIH) to find the location of registered trials conducted under an IND with FDA. The public data can be accessed at www.clinicaltrials.gov. We use the non-public data, which includes a variable indicating whether or not a trial is conducted under an IND with FDA. Table 4 shows the distribution of registered clinicals trials under an IND with FDA for drug and biological products by location. There has been a steady increase in the number of clinical trials registered in US and at least one other ICH country between 2010 and 2020. For example, 25.1% of registered clinical trials on ClinicalTrials.gov were dual registered in the United States and at least one other ICH country in 2010 and rose to 31% by 2020. Overall, about a third of registered IND drug and biological trials were located in at least one ICH country by 2020.

Table 4: Distribution of Registered Clinical Trials for Drug or Biologic Products by Location (IND SUBSET), 2010-2020

Year	US Only	US and at least one ICH	Non-US ICH	Non-ICH	Total
2010	61.3%	25.1%	4.7%	8.8%	2,918
2011	60.7%	27.4%	3.6%	8.2%	2,868
2012	60.6%	27.7%	3.1%	8.6%	2,760
2013	63.6%	25.8%	3.5%	7.1%	2,778
2014	61.9%	26.6%	3.2%	8.3%	2,965
2015	60.7%	27.9%	2.6%	8.8%	2,994
2016	61.8%	27.8%	2.7%	7.7%	2,910
2017	63.1%	29.5%	2.9%	4.5%	3,055
2018	61.4%	30.4%	4.0%	4.3%	3,198
2019	59.7%	31.2%	3.8%	5.3%	3,087
2020	59.1%	31.0%	3.5%	6.3%	3,138

We capture the trend in locations of registered IND studies and project it forward for 2021 to 2030. We calculate the trend by taking the sum of the percent of studies located in US and at least one ICH country and non-US ICH countries to compute the annualized growth rate between 2010 and 2020. We find there to be a 1.3% annualized increase in studies located in this area. We assume the location of these studies remains proportional to 2020 and attribute the increase accordingly (89.8% located in US and at least one ICH country and 10.2% located outside of the US in at least one ICH country). Table 5 shows the expected location of registered IND studies for 2021 to 2030. By 2030, 39.5% of studies are assumed to be located in the US and at least one ICH country or located outside of the US in at least one ICH country.

Table 5. Expected Location of IND studies for Drug and Biologic Products in 2021–2030 with a 1.3 Percent Growth Rate

Year	US only or Non-ICH Country	US and at least one ICH Country	Non-US ICH Country
2021	65.0%	31.4%	3.6%
2022	64.5%	31.8%	3.6%
2023	64.1%	32.3%	3.7%
2024	63.6%	32.7%	3.7%
2025	63.1%	33.1%	3.8%
2026	62.6%	33.6%	3.8%
2027	62.1%	34.0%	3.9%
2028	61.6%	34.5%	3.9%
2029	61.1%	34.9%	4.0%
2030	60.5%	35.4%	4.0%

Using this approach, the implied assumption is that the number of IND registered studies that were conducted in the United States and at least one other ICH country or in at least one ICH country outside the United States is a proxy for the number of sponsors that submit reports to multiple regulatory authorities and will benefit from the DSUR. If

this assumption is an underestimate, then the benefits of this rule will be underestimated, and costs will be overestimated. If this assumption is an overestimate, then the benefits of this rule will be overestimated, and costs will be underestimated. We request comment on this assumption.

1. Estimated Reduction in Labor Resources

To estimate the reduction in labor resources, we first assume that preparing an IND annual report that meets the current regulatory requirements would take 360 hours and that these labor hours are allocated among clerical (25 percent), statistical (25 percent), and regulatory affairs activities (50 percent) (76 FR 4914 at 4916 and 75 FR 59935 at 59958). That is, to prepare the current IND annual report, the estimated number of hours among clerical, statistical, and regulatory affairs activities are, respectively, 90 (360 x 0.25), 90 (360 x 0.25), and 180 (360 x 0.50). Compared to the baseline, FDA assumes that preparing the proposed FDA DSUR would require an additional 5 to 20 percent of the time (or 18 to 72 hours) currently allocated to these activities. FDA seeks comments on this assumption. Thus, the estimated total number of hours required to prepare the proposed FDA DSUR would range from 378 hours (360 x 1.05) to 432 hours (360 x 1.20). Table 6 presents the hours allocated by activity for an existing report as well as the estimated number of labor hours that may be incurred to prepare the proposed FDA DSUR.

Table 6. Estimated Labor Hours to Prepare the IND Annual Report and the Proposed FDA DSUR

Cost Factor	Time Consumed (Percent)	Baseline Labor Hours to Prepare IND Annual Report	Labor Hours to Prepare Proposed FDA DSUR		
			Small	Moderate	Large
			5%	10%	20%
Clerical	25%	90	95	99	108
Statistician	25%	90	95	99	108
Regulatory Affairs	50%	180	189	198	216
Total	100%	360	378	396	432

Note: Totals may not sum up because of rounding.
Sources: 75 FR 59935 at 59958 and 75 FR 4914 at 4916.

The cost savings brought about by harmonization result from a reduction in labor hours used to prepare multiple reports to different regulatory authorities. Prior to the implementation of the proposed FDA DSUR, FDA assumes that sponsors who write multiple reports incur an additional 75 percent of the number of hours required to submit an IND annual report. In other words, writing multiple periodic safety reports involves 630 hours (1.75 x 360). The proposed FDA DSUR would contain similar content as what would be required in reports to other authorities, but the information required will not be entirely the same. Therefore, sponsors may still need to prepare multiple reports to submit to other regions, although the time required to prepare the reports may be reduced since there will be greater overlap in the content of the reports. As a result of this proposed regulation, we assume that sponsors who write multiple reports would incur an additional 25 percent of the number of hours required to submit the proposed FDA DSUR. The reduction in labor hours would be the difference between the hours incurred in preparing multiple reports prior to and after the implementation of the proposed FDA DSUR, accounting for the additional cost to prepare the DSUR relative to the IND annual report. Table 7 presents the estimated decrease in the number of labor hours arising from

harmonization by activity. We note that "Small," "Moderate," and "Large" denote the additional time burden of 5, 10, and 20 percent, respectively.

Table 7. Estimated Labor Hours to Prepare Multiple Periodic Safety Reports

Activity	Labor Hours to Prepare Multiple Reports to Different Regulatory Authorities				Range of Reduction in Labor Hours from Harmonization		
	Multiple Safety Reports Prior to Proposed FDA DSUR	Multiple Safety Reports After Proposed FDA DSUR					
		Small	Moderate	Large	Small	Moderate	Large
Clerical	158	118	124	135	39	34	23
Statistician	158	118	124	135	39	34	23
Regulatory Affairs	315	236	248	270	79	68	45
Total (hours)	**630**	**473**	**495**	**540**	**158**	**135**	**90**

Note: "Small," "Moderate," and "Large" denote the additional time burden of 5, 10, and 20 percent required to prepare the Proposed FDA DSUR relative to the baseline IND Annual Report.

To determine the estimated savings in reduced labor, activities related to the preparation and the submission of the proposed FDA DSUR are valued using 2020 median wages plus benefits and other indirect costs as reported by the U.S. Department of Labor's Bureau of Labor Statistics (Ref. 11) for Pharmaceutical and Medicine Manufacturing (North American Industry Classification System (NAICS) code 325400). Specifically, FDA uses wage information from the standard occupational classification (SOC) system as follows: office and administrative support (SOC 43-0000) for clerical activities, computer mathematical occupations (SOC 15-2041) for statisticians, and management occupations (SOC 11-0000) for activities related to regulatory affairs. Accounting for benefits and other indirect costs, the wage rate is $44.54 for clerical staff, $100.32 for statisticians, and $134.30 for regulatory affairs managers. FDA further assumes that labor hours required for other non-FDA periodic safety reports are valued in U.S. wages. If reports submitted to other regulatory authorities are prepared at a lower

cost, benefits would be overestimated. Likewise, costs would be overestimated if reports are submitted to other regulatory authorities at a higher cost.

Using the labor hour allocations under current regulations presented in Table 7, we estimate that the total cost to sponsors submitting multiple and varying periodic safety reports is $65,120 ([$44.54 x 158] + [$100.32 x 158] + [$134.30 x 315]). The preparation cost of preparing multiple safety reports under the proposed regulation ranges from $48,840 ([$44.54 x 118] + [$100.32 x 118] + [$134.30 x 236]) to $55,817 ([$44.54 x 135] + [$100.32 x 135] + [$134.30 x 270]). These costs are summarized in Table 8.

Table 8. Unit Costs of Preparing Multiple Periodic Safety Reports

Activity	Wage Rate (per hour)	Estimated Preparation Costs			
		Multiple Safety Reports Prior to Proposed FDA DSUR	Multiple Safety Reports After Proposed FDA DSUR		
			Small	Moderate	Large
Clerical	$44.54	$7,037	$5,261	$5,512	$6,013
Statistician	$100.32	$15,851	$11,850	$12,415	$13,543
Regulatory Affairs	$134.30	$42,305	$31,728	$33,239	$36,261
Total		**$65,192**	**$48,840**	**$51,166**	**$55,817**

Note: "Small," "Moderate," and "Large" denote the additional time burden (e.g., 5, 10, and 20 percent) required to prepare the Proposed FDA DSUR relative to the baseline IND Annual Report.

2. Summary of Estimated Benefits

In estimating the annual benefits associated with a decrease in labor hours for multiple reports to regulatory authorities, FDA assumes that sponsors submit periodic safety reports to multiple regulatory authorities for an increasing proportion of the total IND annual reports received each year as previously discussed and displayed in Table 5. FDA tracks annual report submissions in the DSUR format. Using internal data, we estimate that 24 percent of sponsors are voluntarily submitting in DSUR format. Thus,

we subtract 24 percentage points from the percent of sponsors assumed to be submitting to multiple regulatory bodies in each of the low, primary, and high estimates.

We use ClinicalTrials.gov data to calculate the number of countries that registered IND clinical trials are located in. We include only studies located in ICH countries, count only countries that are in ICH, exclude studies located only in the United States, and exclude the US from the total count of countries. We exclude United states because we assume sponsors are already submitted safety reports to the FDA if they have an IND for the trial and include only ICH countries in the total count because we assume they accept DSUR. Table 9 shows the number of country distribution for clinical trials located in ICH countries, excluding the US. The majority of studies are located in one country (35.3%). We calculate the weighted average number of countries that trials are located in to be 3.34 countries. We then use this weighted average to scale the per report harmonization benefit received by sponsors submitting reports to multiple regulatory authorities.

Table 9: Number of Country Distribution for Clinical Trials Located in ICH Countries (Excluding US)

Number of Countries	Count	Percent	Cumulative Distribution
1	3,688	35.3%	35.3%
2	1,748	16.8%	52.1%
3	1,361	13.0%	65.1%
4	883	8.5%	73.6%
5	689	6.6%	80.2%
6	478	4.6%	84.8%
7	367	3.5%	88.3%
8	324	3.1%	91.4%
9	231	2.2%	93.6%
10	193	1.8%	95.5%
11	132	1.3%	96.7%
12	115	1.1%	97.8%
13	67	0.6%	98.5%
14	61	0.6%	99.1%
15+	98	0.9%	100.0%
Total	10,435	100.0%	100.0%

Note: The 'Number of Countries' count is truncated at 15. Any trial with countries beyond 15 is included in the count of '15+'.

Table 10 shows the expected number of report submissions from 2021 to 2030 under the assumption of an increasing trend in reports submitted of 4.4 percent per year and an increasing trend in studies located in the US and at least one other ICH country or outside of the US in an ICH country of 1.3 percent per year. Thus, we estimate that 1,279 reports are submitted to multiple regulatory authorities in 2021 and 2,747 reports are submitted to multiple regulatory authorities in 2030 (as our primary estimate). We estimate the savings from greater harmonization as a result of reduced labor hours for each year by multiplying the number of reports submitted to multiple regulatory authorities in that year by the weighted average of regulatory authorities the reports are

submitted to by the difference in total unit costs of preparing multiple periodic safety reports before and after the FDA Proposed DSUR, as shown in Table 8. For example, in 2021, we estimate the cost savings to range from $83.09 million (1,528 reports x 3.34 regulatory authorities x [$65,120 - $48,840]) in the high estimate to $32.00 million (1,030 reports x 3.34 regulatory authorities x [$65,120 - $55,817]) in the low estimate. In 2030, we estimate the cost savings to range from $171.83 million (3,160 reports x 3.34 regulatory authorities x [$65,120 - $48,840]) to $72.52 million (2,334 reports x 3.34 regulatory authorities x [$65,120 - $55,817]).

Table 10 Expected Report Submissions to FDA Only and FDA and Another Regulatory Authority for 2021–2030

Year	Number of Periodic Safety Reports						
	Total	FDA Only			FDA and Another Regulatory Authority		
		Low	Primary	High	Low	Primary	High
2021	13,883	9,521	9,272	9,023	1,030	1,279	1,528
2022	14,494	9,879	9,616	9,352	1,137	1,400	1,663
2023	15,132	10,249	9,971	9,692	1,251	1,529	1,808
2024	15,797	10,632	10,337	10,043	1,374	1,669	1,963
2025	16,493	11,028	10,716	10,404	1,507	1,818	2,130
2026	17,218	11,437	11,107	10,777	1,649	1,979	2,309
2027	17,976	11,859	11,510	11,161	1,803	2,151	2,500
2028	18,767	12,296	11,926	11,557	1,967	2,336	2,706
2029	19,593	12,746	12,356	11,965	2,144	2,535	2,925
2030	20,455	13,211	12,798	12,385	2,334	2,747	3,160

Present value and annualized benefits are presented in Table 11. Over a 10 year period, present discounted value of total benefits ranges from $336.15 million to $828.74 million at a 7 percent discount rate, and $420.00 million and $1,032.24 million at a 3

percent discount rate. Our primary estimates are $607.29 million at a 7 percent discount rate and $757.38 million at a 3 percent discount rate. The annualized value of benefits at a 7 percent discount rate ranges from $47.86 million to $117.99 million with a primary estimate of $86.46 million. The annualized value of benefits at a 3 percent discount rate ranges from $49.24 million to $121.01 million with a primary estimate of $88.79 million.

Table 11. Present Value and Annualized Benefits over 10 Years [1]

	Discount Rate	Low	Primary	High
Present Discounted Value of Total Benefits	7%	$336.15	$607.29	$828.74
	3%	$420.00	$757.38	$1,032.24
Annualized Value of Total Benefits	7%	$47.86	$86.46	$117.99
	3%	$49.24	$88.79	$121.01

[1] Values are shown in millions of dollars using 2020 dollar values

Additionally, as shown in Table 4, it is estimated that the inventory of clinical trials registered and conducted under an IND in an ICH country has steadily increased since 2010. Thus, as sponsors increasingly conduct clinical trials abroad and are required to submit different periodic safety reports to FDA and other regulatory authorities that accept the ICH DSUR, we estimate that the savings for sponsors from the greater harmonization of periodic safety reports may also increase.

F. Costs of the Proposed Rule

Costs would arise from the additional labor needed to generate additional information that is not contained in the current annual report. The proposed rule would require all sponsors to submit an annual report including, among other things, a cumulative summary of pertinent safety information as well as safety information from all studies conducted on behalf of the sponsor evaluating any dosage form of the drug or its drug substance, whether conducted under an IND or not, information from studies not

conducted by the sponsor, information from other relevant sources (including safety findings from published literature), and integrated analyses of safety information. Additionally, sponsors of INDs who submit hard copies of the proposed annual report would also incur additional printing and shipping costs.

1. Estimated Increase in Labor Costs

Above, we estimate the expected total sponsors submitting annual reports to FDA only each year (See Table 10). These sponsors would incur additional labor costs to develop the added content required by the proposed FDA DSUR. It is possible that the required additional labor would decline as sponsors implemented the processes necessary to create the proposed FDA DSUR and became more efficient in doing so. However, in this analysis, we assume that the additional labor required to prepare the proposed FDA DSUR does not change from year to year, thus possibly overstating these costs over time.

The proposed requirements for reporting would involve more labor for data and statistical analyses and more report-writing activities. As discussed in the baseline section, we estimate that the existing IND annual report takes 360 hours to prepare. With the proposed rule, if finalized, sponsors would incur between 18 hours (378 minus 360) and 72 hours (432 minus 360) of additional labor to prepare the proposed FDA DSUR. Valuing additional labor hours by using 2020 median wages plus benefits and other indirect costs (Ref. 14), we estimate that sponsors would incur an additional cost per report ranging from $1,933 ([$44.54 x 5] + [$100.32 x 5] + [$134.30 x 9]) to $7,442 ([$44.54 x 18] + [$100.32 x 18] + [$134.30 x 36]) (see Table 12). The additional cost of labor for the annual estimated reports affected by the proposed rule is calculated by multiplying the number of reports submitted to FDA only in that year (see Table 10) by

the additional cost per report as shown in Table 12. For example, in 2021, the primary estimate for the additional labor cost ranges from $17.92 million ($1,933 x 9,272) to $69.00 million ($7,442 x 9,272). In 2030, the primary estimate for the additional labor cost ranges from $24.74 million ($1,933 x 12,798) to $95.24 million ($7,442 x 12,798). We include the incremental costs for the reports submitted to multiple regulatory authorities in the benefits section.

Table 12. Estimated Additional Industry Labor Hours and Costs Per Proposed FDA DSUR

Cost Factor	Wage Rate (per hour)	Additional Labor Hours (per proposed FDA DSUR)			Additional Cost (per proposed FDA DSUR)		
		Low	Primary	High	Low	Primary	High
Clerical	$44.54	5	9	18	$223	$401	$802
Statistician	$100.32	5	9	18	$502	$903	$1,806
Regulatory Affairs	$134.30	9	18	36	$1,209	$2,417	$4,835
Labor Cost Per Report		18	36	72	$1,933	$3,721	$7,442

2. Estimated Increase in Printing and Shipping Costs

The costs associated with printing and shipping reports to FDA would depend on the number of additional pages printed and mailed and whether sponsors choose to submit the annual reports electronically via the electronic common technical document (eCTD) system. We note that once a sponsor files the report electronically, subsequent submissions must also be filed electronically. FDA's CDER reported that, as of the end of the 2020 calendar year, 85 percent of annual reports were submitted electronically. Thus, FDA estimates printing and shipping costs under the assumption that 85 percent of the expected annually submitted reports will be filed electronically. For example, in 2021, printing and shipping costs are estimated for 2,082 reports (13,883 x 0.15). In

2030, printing and shipping costs are estimated for 3,068 reports (20,455 x 0.15) This estimated cost may be overstated, because it assumes that the electronic submission rate does not increase over time.

FDA further assumes that the proposed FDA DSUR would require up to 475 additional pages, or weigh approximately 5 additional pounds.[6] These numbers are based on estimates on the number of pages for the current IND annual report and under the assumption that a typical 500-page ream of paper weighs approximately 5 pounds (namely, that 1 pound of paper would include about 100 pages).

The estimated printing cost per report ($14.25) is calculated as the number of additional pages multiplied by the cost per page of $0.03 (Ref. 12). An additional mailing cost of $44.25 is determined by calculating the difference between mailing an overnight package weighing 6 pounds at a cost of $154.20 and mailing another package weighing 1 pound at a cost of $109.95 through a standard express courier and shipping it to a destination that is at least 1,800 miles from the original location (Ref. 13). Printing and mailing costs per report are estimated at $58.50 ($14.25 + $44.25). We calculate the total printing and shipping costs in each year from 2021 to 2030 by summing over the expected annual number of reports that we estimate would be submitted in paper form each year and would thereby incur printing and mailing costs.

3. Costs to Read the Rule

Individuals from affected entities will need to devote time to reading and understanding this proposed rule. We assume an average of one manager for each sponsor facility will read the rule. At an adult average reading speed of 200-250 words

[6] The periodic safety update report (PSUR), which is the periodic safety report filed for marketed products, could have from 125–150 pages to 60–1800 pages for products with a long approval history.

per minute, we estimate that each reader will spend about 1 hour. We value the opportunity cost of one hour using the mean hourly wage of a regulatory affairs manager, which is doubled to account for benefits and other indirect costs as described above. We estimate the time spent learning about the rule at a cost of $134.30 per facility. We assume this is a one-time cost incurred in the first year. Thus, multiplying this estimate by the 13,883 expected reports from sponsors in 2021 yields a total one-time cost for reading the rule of $1,864,502.

4. Cost to Government

FDA will incur incremental costs to review the additional information in the proposed FDA DSUR. As previously referenced above, FDA assumes that the proposed FDA DSUR would require up to 475 additional pages. We assume that these pages are double spaced and contain an average of 250 words per page. Using FDA's central estimate of reading speed of 225 words per minute, this is an additional 8.8 hours per report. To value FDA employee time, we use internal data from our Fully Loaded Full Time Employee Cost Model. We value FDA employee time at $142.20 per hour and estimate a primary value for the additional cost to government to be $1,251 per report. Table 13 shows FDA cost per report using a range of reading speeds from 200 to 250 words per minute. The government cost per report ranges from $1,126 to $1,407.

Table 13. Estimated Additional Government Labor Hours and Costs Per Proposed FDA DSUR

	Low	Primary	High
Additional Page Count	475	475	475
Words per page	250	250	250
Total words	118,750	118,750	118,750
Reading Speed (words per min)	200	225	250
Labor Hours per report	9.90	8.80	7.92
FDA Time Value	$142.20	$142.20	$142.20
FDA Cost per Report	$1,407.19	$1,250.83	$1,125.75

The additional cost to government for the annual estimated reports affected by the proposed rule is calculated by multiplying the total number of reports submitted to FDA in that year (see Table 10) by the additional cost per report as shown in Table 13. For example, using the primary government cost value in 2021, we estimate the additional government cost to range from $15.63 million ($1,126 x 13,883) to $19.54 million ($1,407 x 13,883). In 2030, we estimate the additional government cost to range from $23.03 million ($1,126 x 20,455) to $28.78 million ($1,407 x 20,455).

5. Summary of Estimated Costs

As shown in Table 12, we estimate that it will cost an additional $1,933 to $7,442 per report for a sponsor to create and submit the proposed FDA DSUR to FDA. We estimate that sponsors will incur a cost of $134.30 on time spent learning about the rule. For the 15 percent of sponsors assumed to be submitting their reports in paper form, we estimate

that it will cost a sponsor an additional $14.25 to print the proposed FDA DSUR and an additional $44.25 to ship the report. Finally, we estimate that FDA will incur a cost of $1,125 to $1,407 per report to review the additional pages of the FDA DSUR (see Table 13). Present value and annualized costs are presented in Table 14. Present value costs over a 10 year period range from $283.96 million to $711.77 million at a 7 percent discount rate, and $348.83 million and $874.18 million at a 3 percent discount rate. Our primary estimates are $429.20 million at a 7 percent discount rate and $527.21 million at a 3 percent discount rate. The annualized cost values of the primary estimates are $61.11 million at a 7 percent discount rate and $61.81 million at a 3 percent discount rate.

Table 14. Present Value and Annualized Costs over 10 Years in Millions of 2020 Dollars

	Discount Rate	Low	Primary	High
Present Discounted Value of Total Costs	7%	$283.96	$429.20	$711.77
	3%	$348.83	$527.21	$874.18
Annualized Value of Total Costs	7%	$40.43	$61.11	$101.34
	3%	$40.89	$61.81	$102.48

G. Analysis of Regulatory Alternatives to the Proposed Rule

The proposed rule seeks to change the format and content of the IND annual report, which would be required to be submitted no later than 60 days from the data lock point. FDA identified the following alternatives to the proposed rule: (1) extend the submission period under the proposed rule to 120 days and (2) require electronic submission of annual reports.

1. Alternative 1: Extend the Submission Period to 120 Days

Under the alternative to submit the FDA DSUR within 120 days of the data lock point, sponsors may be able to improve on their allocation of resources, which could result in savings and reducing labor costs. However, extending the time for submission

would postpone the benefits of having access to information that is crucial to assess the risks associated with clinical trials and the safety of the human subjects. FDA does not have data from which to estimate potential reductions in costs or savings and asks for detailed comments and data on this issue.

2. Alternative 2: Requiring Electronic Submissions of Annual Reports

Electronic submission of IND annual reports has increased as a fraction of all submissions. As of the end of the 2020 calendar year, 85 percent of annual reports were submitted electronically. Under this alternative, we would require electronic submissions for all IND annual reports. As a result, printing and mailing costs would be zero, and benefits would remain unchanged. Because this scenario eliminates shipping and mailing costs, which are a small portion of the overall costs and experienced by only the 15% of annual reports not currently electronically submitted, the estimated benefits and costs remain relatively unchanged from the main analysis.

Table 15. Present Value and Annualized Benefits and Costs Assuming a 100% Electronic Submission Rate in Millions of 2020 Dollars

Costs	Discount Rate	Low	Primary	High
Present Discounted Value of Total Costs	7%	$282.98	$428.21	$710.79
	3%	$347.62	$526.00	$872.97
Annualized Value of Total Costs	7%	$40.29	$60.97	$101.20
	3%	$40.75	$61.66	$102.34
Benefits				
Present Discounted Value of Total Benefits	7%	$336.15	$607.29	$828.74
	3%	$420.00	$757.38	$1,032.24
Annualized Value of Total Benefits	7%	$47.86	$86.46	$117.99
	3%	$49.24	$88.79	$121.01

H. Sensitivity Analysis

1. No Growth Trend in the Submission Rate of Annual Reports

The annual benefits and costs summarized in section II.C are estimated under the assumption that the number of annual reports increases at a rate of 4.4 percent each year. In this section, FDA estimates the benefits and costs under the assumption that the number of reports remains unchanged over time, with everything else being constant. We use the reported 13,298 annual reports from 2020. Relative to the main analysis, annualized benefits and annualized costs are less because there are fewer reports being submitted overall. Thus, there are less harmonization benefits realized as well as less additional preparation costs for submitting to FDA only and FDA employee time to review additional reports. Table 16 presents the present value and annualized benefits and costs under this scenario assuming a 7-percent and a 3-percent discount rate over 10 years.

Table 16. Present Value and Annualized Benefits and Costs Assuming No Growth Trend in IND Annual Reports in Millions of 2020 Dollars

Costs	Discount Rate	Low	Primary	High
Present Discounted Value of Total Costs	7%	$227.60	$344.39	$571.67
	3%	$275.82	$417.35	$692.71
Annualized Value of Total Costs	7%	$32.41	$49.03	$81.39
	3%	$32.33	$48.93	$81.21
Benefits				
Present Discounted Value of Total Benefits	7%	$265.12	$479.96	$655.95
	3%	$326.84	$590.59	$806.09
Annualized Value of Total Benefits	7%	$37.75	$68.34	$93.39
	3%	$38.32	$69.24	$94.50

2. Change in the Distribution of Submissions for Multiple Annual Reports

In this section, we estimate the sensitivity of benefits and costs to changes in the distribution of annual reports that are currently submitted to FDA and to other regulatory authorities. There is uncertainty regarding the number of reports that are submitted to both FDA and to other regulatory Agencies by the same sponsor for the same drug. In this section, we are using an alternative assumption that the percentage of research and development (R&D) spending in the United States and other countries is a proxy for the percentage of reports submitted to FDA and to multiple Agencies by the same sponsor for the same drug. Specifically, we estimate the percentage of DSURs that are submitted to FDA only and to FDA plus other regulatory authorities to be 41 percent and 59 percent of total DSURs submissions, respectively. We assume that 35 percent of sponsors benefit from harmonization (59% submitting to FDA and multiple agencies minus 24% of reports that are voluntarily submitted in DSUR format). These estimates are based on R&D expenditures reported in 2008 by pharmaceutical companies in the United States (41 percent) and in Europe and Japan (59 percent) (Ref. 14). The implied assumption is that the percentage of R&D expenditures in the United States, Japan, and Europe parallels the distribution of sponsors developing drugs subject to the annual reporting requirements of FDA only or also of other regulatory authorities. We request comment on this assumption.

Under this scenario, the distribution of reports that are submitted to multiple regulatory authorities is greater than the distribution in the baseline. We further assumed that the distribution of reports that are submitted to multiple regulatory authorities does

not change over time. Hence, we would expect the benefits to be noticeably higher than the baseline estimates. Moreover, we would expect costs to decrease, because the number of FDA DSURs that would incur additional costs would be less than the baseline. Table 17 presents the estimated annual benefits and costs under the new distribution. As expected, the results show that, if a larger share of the reports is submitted to multiple regulatory authorities, benefits could be larger, and costs could be smaller.

Table 17. Present Value and Annualized Benefits and Costs When Changing the Initial Distribution of Multiple Safety Reports in Millions of 2020 Dollars

Costs	Discount Rate	Low	Primary	High
Present Discounted Value of Total Costs	7%	$280.12	$430.02	$729.87
	3%	$344.48	$529.01	$898.12
Annualized Value of Total Costs	7%	$39.88	$61.23	$103.92
	3%	$40.38	$62.02	$105.29
Benefits				
Present Discounted Value of Total Benefits	7%	$1,266.32	$1,899.47	$2,216.05
	3%	$1,558.80	$2,338.21	$2,727.91
Annualized Value of Total Benefits	7%	$180.30	$270.44	$315.52
	3%	$182.74	$274.11	$319.79

I. International Effects

The requirements of this proposed rule, if finalized, would apply to both sponsors who conduct clinical trials domestically and abroad. The benefits of labor cost savings due to harmonization would apply to both groups. The costs of this proposed rule would be borne by any sponsor; this includes both foreign and domestic firms. The total and net costs estimated in this Preliminary Regulatory Impact Analysis would be shared

by all affected entities, both foreign and domestic. As of 2020, 40.9% of registered clinical trials with an IND were conducted in at least one country outside of the United States. FDA does not have data to separately assess the likely impacts to U.S. and non-U.S. individuals and entities and asks for detailed comments and data on this issue.

III. Initial Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed requirements are unlikely to impose a substantial burden on the affected small entities, we propose to certify that the proposed rule is unlikely to have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

The Small Business Administration (SBA) uses different definitions of what a small entity is for different industries. Using the most recent (2022) SBA size standard definitions, a firm categorized in NAICS code 325412 (Pharmaceutical Preparations) or NAICS code 325414 (Biological Products) is considered small if it employs fewer than 1,250 people (Ref. 15). The most current data on the number of establishments by employee size is available from the 2017 Economic Census (Ref. 16). Table 18 shows that the majority of the establishments have employee sizes by which they would be considered small. Using data at the establishment level implicitly assumes that the

typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

When an individual both initiates and conducts an investigation, and the investigational drug is administered or dispensed under their immediate direction, the role is termed sponsor-investigator.[7] Sponsor-investigators would generally be considered small entities under the SBA standards. Sponsor-investigator clinical trials are generally simpler than industry-sponsored, commercial single-product development trials and generally involve academic researchers (who act as clinical investigators for purposes of FDA regulations). Although academic investigators may be experts in their field, they may often lack funding and knowledge of the complex and evolving area of the clinical trial process and regulatory requirements. By contrast, staff of industry-sponsored clinical trials often have access to knowledge regarding regulatory aspects of product development (Refs. 17 through 19). In the current analysis, we assume that costs and benefits will flow to firms independent of firm size. We request comment from the public on this assumption.

Table 18. Number of Establishments by Employee Size

Description	Pharmaceutical Preparation		Biological Products	
NAICS	325412		325414	
Small by SBA	< 1,250 Employees		< 1,250 Employees	
Number of Employees				
All	1274	100%	331	100%
0-999	976	77%	228	69%
1,000-1,499	23	2%	17	5%
1,500+	275	22%	86	26%

[7] See 21 CFR § 312.3.

B. Description of the Potential Impacts of the Rule on Small Entities

To determine the unit cost as a percentage of the total value of receipts for a typical manufacturer, FDA used data on the total value of receipts, which measure the dollar value of products sold by manufacturing establishments[8], by employment size from the 2017 Economic Census (Ref. 16). The analysis of the effect on small versus large entities is limited by data restrictions imposed by the Census Bureau to safeguard the confidentiality of some establishments. Consequently, the average value of receipts is only presented for all establishments and by employment size for establishments for which data were made available by the Census Bureau.

Table 19 presents the average value of receipts for establishments in NAICS code 325412 by employment size. The average value of receipts for entities that employ 0 to 4 is nearly $1.25 million; for entities with 5 to 9 employees, it is about $3 million.[9] We estimate that the average annual cost of about $4,000 per IND annual report as a percentage of average value of receipts for small entities in pharmaceutical preparation may be between 0.00 percent and 0.31 percent. Using the high cost estimate of $7,500 per IND annual report, we estimate the average annual cost as a percentage of the value of receipts for small entities to be between 0.00 percent and 0.61 percent.

[8] This estimate may overstate the impact on investigators that are not manufacturers.
[9] These estimates from the 2017 Economic Census are adjusted for inflation to 2020 dollars using the GDP Deflator.

Table 19. Estimated Costs for a Typical Small Entity: Pharmaceutical Preparation (NAICS 325412)

Number of Employees	Number of Establishments	Average Value of Receipts	One-time Cost	One-time Cost as a % of Receipts	Primary Annual Costs	Annual Cost as a % of Average Receipts
All	1,274	$127,979,795	$134	0.000%	$3,780	0.003%
0-4	334	$1,237,303	$134	0.011%	$3,780	0.305%
5-9	137	$2,932,232	$134	0.005%	$3,780	0.129%
10-19	113	$9,469,779	$134	0.001%	$3,780	0.040%
20-49	126	$12,621,381	$134	0.001%	$3,780	0.030%
50-99	68	$29,518,816	$134	0.000%	$3,780	0.013%
100-199	74	$45,256,933	$134	0.000%	$3,780	0.008%
200-499	74	$74,442,234	$134	0.000%	$3,780	0.005%
500-999	50	$123,445,600	$134	0.000%	$3,780	0.003%
1,000-1,499	23	$85,824,212	$134	0.000%	$3,780	0.004%
2,500+	275	$505,383,649	$134	0.000%	$3,780	0.001%

Table 20 presents the average value of receipts for establishments in NAICS code 325414 by employment size. The average value of receipts for entities that employ 0 to 4 employees is about $1.6 million; for entities with 5 to 9 employees is about $6 million. We estimate that the average annual cost of about $4,000 per IND annual report, as a percent of the average value of receipts for these entities, is between 0.00 and 0.24 percent. Using the high cost estimate of $7500 per IND annual report, we estimate the average annual cost as a percentage of the value of receipts for small entities to be between 0.00 percent and 0.47 percent.

The Agency tentatively concludes that this rule is unlikely to have a significant impact on a substantial number of small entities. We request comment on this conclusion and the potential impacts on small sponsors not represented in this Census data.

Table 20. Estimated Cost for a Typical Small Entity: Biological Products (NAICS 325414)

Number of Employees	Number of Establishments	Average Value of Receipts	One-time Cost	One-time Cost as a % of Receipts	Primary Annual Costs	Annual Cost as a % of Average Receipts
All	331	$105,464,336	$134	0.000%	$3,780	0.004%
0-4	72	$1,603,630	$134	0.008%	$3,780	0.236%
5-9	37	$5,991,960	$134	0.002%	$3,780	0.063%
10-19	27	$9,008,025	$134	0.001%	$3,780	0.042%
20-49	32	$12,600,444	$134	0.001%	$3,780	0.030%
50-99	25	$21,909,442	$134	0.001%	$3,780	0.017%
100-199	20	$40,670,671	$134	0.000%	$3,780	0.009%
200-499	5	$84,461,364	$134	0.000%	$3,780	0.004%
500-999	10	$123,500,435	$134	0.000%	$3,780	0.003%
1,000-1,499	17	$78,775,944	$134	0.000%	$3,780	0.005%
1,500+	86	$328,315,440	$134	0.000%	$3,780	0.001%

C. Alternatives to Minimize the Burden on Small Entities

An alternative that would present possible reductions in costs, besides those discussed in section II.G, would be to exempt small entities. Exempting small entities from reporting requirements would result in an estimated annual savings of less than 1 percent of the unit cost of the value of receipts for small-sized firms. However, these reporting requirements enable FDA to assess the status of studies being conducted under the IND and, for example, to learn of updates to the general investigational plan for the coming year.

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