DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Good Laboratory Practice for Nonclinical Laboratory Studies; Proposed Rule

Docket No. FDA-2010-N-0548

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

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I. Preliminary Regulatory Impact Analysis

A. Introduction and Summary

1. 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 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe 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 proposed requirements are likely to impose a significant burden on small entities employing fewer than 10 workers in "Dental Equipment and Supplies" (between 1.87 percent and 8.94 percent of average annual sales), we find that the proposed rule would have a significant economic impact on a substantial number of small entities, but the impacts are uncertain.

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 $146 million, using the most current (2015) 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.

2. Summary

This proposed rule would amend the regulations regarding good laboratory practices (GLPs) and would require that nonclinical laboratory studies (sometimes referred to as preclinical studies) follow a complete quality system approach, referred to as a GLP Quality System, when safety and toxicity studies support or are intended to support applications and submissions to FDA. The proposed rule would expand the scope to include all products for which nonclinical laboratory studies are currently conducted that are not explicitly discussed in the current regulations, specifically tobacco products. The proposed expanded scope also includes all applications and submissions under the Federal Food, Drug, and Cosmetic Act that can be supported by the results of nonclinical laboratory studies. In addition, the proposed rule would introduce and modify definitions, terms, and organizational and personnel roles and responsibilities consistent with the implementation of the proposed GLP Quality System and the prevalence of multisite studies. Finally, the proposed rule would incorporate wording consistent with some of the existing domestic and international guidelines, rules or regulations covering good laboratory practices such as those established by the Organisation for Economic Co-operation and Development (OECD).

Costs of the rule, when final, would include annual and one-time costs. Annual costs would include the additional reporting and recordkeeping responsibilities required under the proposed GLP Quality System. One-time costs include reading and understanding the rule,

updating existing Standard Operating Procedures (SOPs), writing new SOPs, and training. Combined, all costs annualized over a ten-year period at a 7-percent discount rate are estimated to range between $34.4 million and $69.3 million, with an average annualized cost of $51.9 million. By contrast, with a 3 percent discount rate, annualized cost would range from $34.2 million to $68.9 million, with an average annualized cost of $51.5 million.

Conducting nonclinical laboratory studies under the proposed GLP Quality System is expected to improve the reliability and quality of the data that support applications and submissions to us, including those applications and submissions that lead to the use of new medical products in first-in-human clinical studies. In addition, the proposed system is conducive to improving compliance and accountability by all involved in the conduct of nonclinical laboratory studies. The costs and benefits are summarized in Table 1 below.

Table 1.--Summary of Benefits, Costs and Distributional Effects of Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2014	7%	10 years	
					2014	3%	10 years	
	Annualized Quantified				2014	7%	10 years	
					2014	3%	10 years	
	Qualitative	The proposed rule would clarify GLP standards to facilitate a more consistent approach and provide greater international consistency. As a result, we anticipate improvements in the integrity and quality of data submitted for FDA review decisions.						
Costs	Annualized Monetized $millions/year	$51.9	$34.4	$69.3	2014	7%	10 years	
		$51.5	$34.2	$68.9	2014	3%	10 years	
	Annualized Quantified				2014	7%	10 years	
					2014	3%	10 years	
	Qualitative							
Transfers	Federal				2014	7%	10 years	

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	Annualized Monetized $millions/year				2014	3%	10 years	
		From:			To:			
	Other Annualized Monetized $millions/year				2014	7%	10 years	
					2014	3%	10 years	
		From:			To:			
Effects	State, Local or Tribal Government: None estimated. Small Business: The proposed requirements would likely impose a significant burden on small entities employing fewer than 10 workers in "Dental Equipment and Supplies" (between 1.87 and 8.94 percent of average annual sales). However, we do not have data on how many of these dental-equipment small entities perform nonclinical laboratory studies to support, or intended to support, an application or submission regulated by us; only such entities would be affected by the rule. Wages: None estimated.							

B. Background and Baseline

Nonclinical laboratory studies, often referred to as preclinical studies when conducted before first-in-human clinical studies, provide safety or toxicity information or both that is essential for the development of FDA-regulated products and help determine the safety of new food ingredients. For drugs administered to animals whose products will be consumed by humans, such studies are critical for determining safe levels of residual drug product. For tobacco products, nonclinical laboratory studies may provide evidence regarding the relative toxicities of new or modified risk tobacco products. Our regulation of the conduct of nonclinical laboratory studies is important to help ensure the quality and integrity of data derived from those studies, the protection of human subjects, and that marketing decisions are based on accurate and reliable data. To help ensure data quality and integrity, nonclinical laboratory studies must comply with the good laboratory practice (GLP) regulations prescribed in Title 21 Code of Federal Regulations, part 58 (21 CFR part 58). The conduct of these studies involves a variety of persons, including sponsors, testing facilities, study directors, contributing scientists, principal investigators, and contracted persons that are also affected by the proposed rule.

Current FDA regulations describing good laboratory practice (GLP) requirements (21 CFR part 58) were developed when nonclinical laboratory studies were less complex. However, nonclinical laboratory studies have grown larger in size (i.e., involve a greater number of persons) and may involve multiple persons in a number of different locations--both foreign and domestic. This added complexity can result in inadequate management of critical elements of nonclinical laboratory studies. During GLP inspections we have found evidence of repeated noncompliance or deficiencies, including organizational or personnel deficiencies. We use GLP-inspection results as a measure of the degree of GLP non-compliance.

We classify results from inspections according to three categories: (1) if there are no issues found, the inspection receives a No Action Indicated classification; (2) problems found during an inspection that do not require regulatory action receive a Voluntary Action Indicated; and (3) more importantly, if we uncover substantial non-compliance with GLP regulations, the inspection is assigned an Official Action Indicated (OAI) classification.[1] Column 3 of Table 2 shows that for all inspections classified between 2007 and 2012 the percentages of inspections resulting in an OAI range from a minimum of 2 percent to a maximum of 12 percent.

Table 2.--GLP Inspections and Their Outcomes

1 Further guidance on this terminology can be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm073059.htm.

Fiscal Year	Number of Classified Inspections	Percent of Classified Inspections with Official Action Indicated (OAI)
2007	55	7%
2008	43	4%
2009	49	12%
2010	81	4%
2011	41	10%
2012	40	2%

Source: Bioresearch Monitoring (BIMO) Metrics, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm261409.htm

Bioresearch Monitoring (BIMO) program data show that most of the deficiencies found during GLP inspections are associated with: organizational or personnel inadequacies; inadequate, incomplete, or lack of study reports or study records; study article or equipment inadequacies; inadequate procedures followed when study deviations occur; inadequate or lack of standard operating procedures or protocol; and animal care inadequacies. Table 3 below shows the number of citations issued during inspections for fiscal years 2006-2012. Organizational and personnel inadequacies include cases such as failure of a study director, quality assurance unit, or testing facility management to fulfill their roles or functions as required by the current regulation. The second most common deficiency found is associated with problems with data, study records or study reports that were not adequately archived, recorded, reviewed, maintained, or completed. Our investigators also found deficiencies with respect to material essential to the study such as test or control articles, equipment, mixtures or reagents. The top three most cited deficiencies account for most of the citations.

Table 3.--Deficiencies Found During GLP Inspections

Citation associated with	2006	2007	2008	2009	2010	2011	2012
Organizational or personnel inadequacies	48	36	30	46	38	50	54
Study reports or study records	29	20	19	35	19	14	15
Test article, equipment, mixtures, or reagents	25	29	9	15	11	12	11
SOPs	12	13	7	8	11	11	12
Study conduct	9	16	10	16	11	7	5
Protocol	16	2	5	6	4	1	3
Animal care	7	5	5	5	2	2	1

Source: TURBO Inspectional Observation Datasets of Bioresearch Monitoring (BIMO) GLP Inspections, Fiscal Years 2006-2012, http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm.

Comments to the December 10, 2010 Advanced Notice of Proposed Rulemaking (ANPRM 2010) (Docket No. FDA-2010-N-0548) supported the need to revise and clarify roles and responsibilities of those involved in the conduct of nonclinical laboratory studies, including management, the quality assurance unit, the sponsor, the study director, the collaborating scientists, and the other entities involved in the conduct of a nonclinical laboratory study. Several comments called for FDA GLP regulations to be aligned with other existing regulations or guidelines such as Environmental Protection Agency (EPA) GLPs (Ref. 1), the Organisation for Economic Co-operation and Development (OECD) Principles of GLPs (Ref. 2), or the Animal Welfare Act. Many comments requested that we provide further clarification with respect to documentation and retention of data, study reports and study records. Comments from stakeholders recognized the importance of having a GLP quality system. However, some comments suggested that the ISO 9001, in addition to being too prescriptive, was not adequate for the conduct of nonclinical laboratory studies. Instead, comments recommended that we require a flexible system such as the one required by OECD Principles of GLPs or to model it after 21 CFR part 820 (manufacturing quality system requirements for medical devices). The

comments concluded that additional oversight by FDA on animal welfare could result in duplicative efforts. Finally, commenters indicated that allowing us to review findings on quality assurance inspections could compromise candid disclosure and undermine the intended role of the quality assurance unit.

C. Need for Regulation

Based on outdated practices, our existing GLP regulations fail to reflect the current conduct of nonclinical laboratory studies, especially for multisite studies. This can create confusion about how we expect people to conduct these studies. Some provisions written prior to the widespread use of electronic media require persons conducting nonclinical laboratory studies to maintain paper records, requirements that hamper the efficient use of resources. Our current GLP regulations create a potential institutional failure that inhibits a modern quality system approach to conduct these studies. Modernizing the GLP regulations and providing a flexible framework to promote use of a complete quality system approach would inform persons conducting nonclinical laboratory studies of our expectations and reduce uncertainty. With a flexible framework, we allow laboratories to implement a GLP Quality System to efficiently use their resources. We expect that studies conducted under a complete quality system would generate consistently higher quality data, improving the data integrity of studies used to support regulatory decisions about product safety.

D. The Proposed Rule

Incorporating stakeholder feedback and our experience, the proposed rule would require the implementation of the proposed GLP Quality System's full quality system approach. First, the proposed rule would clarify and define new terms, roles, and responsibilities for all persons involved in the conduct of nonclinical laboratory studies to accommodate current practice, i.e.

address multisite studies, and to be more consistent with other existing domestic and international regulations and guidelines. This also involves proposed requirements for additional information to be included in existing standard operating procedures (SOPs) as well as new SOPs needed to implement the proposed GLP Quality System. It also proposes implementing a 'checks and balances' system to further ensure integrity of the data; GLP compliance; and proper recording and retention of study materials, documents, and reports. Second, it proposes that all entities involved in the conduct of a nonclinical laboratory study such as a sponsor, testing facility, contributing scientist, the quality assurance unit (QAU), and contracted person are explicitly defined as are their roles and responsibilities. As part of this, all persons who conduct a phase of the study would be subject to inspection and disqualification.

Third, the proposed rule would expand the scope of current regulations to include all non-clinical laboratory studies for safety or toxicity or both that support an application or submission to us. This includes applications involving tobacco products and other products such as abbreviated new animal drug applications, applications for conditional approval of new animal drugs for minor use or minor species, authorizations to market edible products from experimental animals, Humanitarian Device Exemptions (HDEs), and premarket submissions (510(k)s). Thus, by proposing to expand regulatory oversight, the proposed rule would address gaps in current GLP regulations.

Further consistency of FDA's GLP requirements with EPA's GLP regulations and the OECD Principles of GLP can help reduce expenditures and required resources for those entities that already have processes in place to meet the requirements of either or both of them. Clarifying roles and responsibilities for those involved in the conduct of nonclinical laboratory studies can improve the integrity and quality of the data submitted in support of applications and submissions

to us. A more consistent global approach can facilitate the conduct of nonclinical laboratory studies and help to enhance compliance.

E. Benefits of the Proposed Rule

Given the complexity of the nonclinical laboratory studies enterprise and lack of data, we cannot quantify or monetize benefits arising from this rule. We seek comments or data to support (quantify or monetize) the benefits of this rule. Lacking data to monetize the potential benefits, we provide a summary of comments received from stakeholders (FDA Docket 2010-N-0548) to describe what some of the benefits of the proposed rule could entail. Review of the comments indicates that there is significant support for revising the current regulation. The most common reasons given to support revisions to GLP regulation (21 CFR part 58) included: the inadequacy of the current regulations, the need for clarification of roles and responsibilities of all entities involved in the conduct of clinical laboratory studies, and the alignment of GLP regulations with other international regulations. Some comments also suggested that to some entities, revisions to GLP regulations would reflect current practice.

Many comments suggested that we revise the provisions pertaining to organizational structure or personnel roles, international consistency, study records, study data, and study material. Such revisions would modernize our regulations to better match current business practices and remove some regulatory obstacles that could hamper efficient use of resources (e.g., requiring paper records rather than accepting electronic records).

Beside potential gains in efficiency, the proposed rule could provide additional benefits from the implementation of the proposed GLP Quality System. A more consistent alignment of our regulations with other existing international and domestic GLP regulations and guidance can further reduce duplicative efforts or allocation of resources. This in turn could reduce

development costs and improve compliance. We believe that implementing the proposed GLP Quality System will help ensure uniformity, consistency, reliability, quality, reproducibility, and integrity in all aspects of a nonclinical laboratory study, which will result in improvements in the quality and integrity of data submitted in support of applications and submissions to us.

Nonclinical laboratory study data form the basis for our characterization of potential hazards and risks that humans could be exposed to during an investigational study or can help us understand risks that emerge after years of marketing an approved product. For example, nonclinical laboratory studies help determine the safety of new food ingredients. Nonclinical laboratory studies are also critical for determining safe levels of investigational drugs that may be used in human subjects participating in clinical studies. Nonclinical laboratory studies also provide certain information on the safety and effectiveness of medical devices that would not be possible, or ethical, to test in humans during the development stage, e.g., heart valves. And, for tobacco products, nonclinical laboratory studies help in providing evidence of the relative toxicity of new or modified risk tobacco products.

We request detailed comment on the potential benefits of the proposed rule.

F. Costs of the Proposed Rule

The proposed requirements would result in annual costs from reporting and recordkeeping. In addition, we estimate one-time costs from reading and understanding, updating SOP and writing new SOPs, and training. These costs are in turn discussed in the subsections that follow.

3. Reporting Costs

The proposed rule proposes additional reporting responsibilities from various entities involved in the conduct of a nonclinical laboratory study to enhance the information that is

essential to implement the proposed GLP Quality System, e.g., providing information on test, control, and reference article characterization, reporting results of process-based inspections, and adequate reporting of study deviations and study reports. Table 4A below briefly describes the additional reporting requirements, and the proposed entity responsible for ensuring the requirement is fulfilled.

Table 4A.--Additional Reporting Responsibilities Proposed by the Rule

Main Entity Responsible*	Additional Reporting Responsibility
Sponsor	R01. Provide test, control, and reference article characterization and risk information
	R02. Provide nonclinical laboratory study report in support of applications and submissions
Quality Assurance Unit (QAU)	R03. Expanded content of QAU statement in final study report
Management with Executive Responsibility	R04. Management report of actions taken when a process-based inspection reveals problems
	R05. Management report of personnel deviations from protocol
Study Director	R06. Expanded contents of final study report
	R07. Compliance statement by study director appended to final study report
	R08. Summary report of close-out for discontinued studies
Contributing Scientists or Principal Investigators	R09. Reports by independent contributing scientist(s) to study director or principal investigator
	R10. Study deviation reports from principal investigator to study director
	R11. Signed and dated compliance statement, final study reports and amendments, if applicable, from principal investigator to study director

Note: * Task may involve other assistance such as clerical.

With input from the Society for Quality Assurance (SQA) and other experts in the field, we estimated the number of entities (responders), the annual reporting frequency, and total labor hours associated with each of the additional proposed requirements. In estimating the value of labor resources, we assume 25 percent of the total estimated labor time is allocated to clerical assistance. We seek comments or data to support other assumptions on this issue.

Because the composition of the entities affected cover manufacturers across all product areas regulated by FDA, we use the median hourly wage rate for industry sectors 31, 32, and 33 as reported by the Bureau of Labor Statistics for 2014 (Ref. 3) to value labor hours. Reporting responsibilities for the sponsor or other entities with a managerial role are valued using "Management Occupations," (Standard Occupation Code (SOC), 110000) at $52.80 per hour. Labor hours for contributing scientists or investigators are valued using an average of the wage rate for the following occupations "Statisticians" (SOC 152041, hourly wage of $45.71), "Chemists and Material Scientists" (SOC 192030, hourly wage rate of $35.82), "Veterinarians" (SOC 291131, hourly wage rate of $34.26), "Biochemists and Biophysicists" (SOC 191021, hourly wage rate of $40.92), "Environmental Scientists and Specialists including Health" (SOC 192041, hourly wage rate of $41.83), "Biological Scientists" (SOC 191020, hourly wage rate of $37.44), "Animal Scientists" (SOC 191011, hourly wage rate of $34.46). The average wage rate among these occupations is $39.90. Clerical assistance is valued using SOC 434071 ("File Clerks") reported at $14.42 per hour. Before calculating the estimated labor cost we multiply the reported wage rate by 2—a commonly used multiplier—to adjust the median hourly wage rate for benefits and overhead.

Estimated total cost for each of the additional proposed responsibilities is determined by multiplying the number of entities affected by the annual reporting frequency per entity affected

and the unit labor cost (see Table 4B). Unit cost of labor for each reporting responsibility is calculated as the labor hours per entity involved in the specific reporting task times the wage rate. For instance, total cost of $0.57 million for reporting responsibility code R01 ("Provide test, control, and reference article characterization and risk information") is calculated as follows: 1,316 respondents x 5 average annual responses per respondent x (0.75 hours x $105.60 per hour + 0.25 hours x $28.84 per hour). The reporting costs for the remaining reporting responsibilities, R02-R12, are calculated in a similar fashion. Adding the estimated costs across all entities affected provides an estimated annual cost of the proposed rule of $5.8 million. We note that even though Table 4B provides costs disaggregated by entity responsible; these costs will be mainly paid by the sponsor funding the nonclinical laboratory study. We request comments with data regarding the average annual reporting per entity as some entities may vary from this expected average.

Table 4B.--Estimated Reporting Costs of the Proposed Rule

Main Entity Responsible*	Additional Reporting Responsibility	Number of Entities Affected	Average Annual Reporting	Labor Hours (per response)			Unit Cost ($)	Total Cost ($millions)
				Total Hours per Response	Main Entity	Clerical Assistant		
Sponsor	R01	1,316	5	1	0.75	0.25	$86.41	$0.57
	R02	10	1	15	11.25	3.75	$1,296.15	$0.01
Quality Assurance Unit (QAU)	R03	300	60.25	0.25	0.19	0.06	$21.60	$0.39
Management with Executive Responsibility	R04	10	2	5	3.75	1.25	$432.05	$0.01
	R05	300	10	0.5	0.38	0.13	$43.21	$0.13
Study Director	R06	300	60.25	2	1.50	0.50	$172.82	$3.12
	R07	300	60.25	0.5	0.38	0.13	$43.21	$0.78
	R08	300	2	2	1.50	0.50	$172.82	$0.10
Independent Contributing Scientist or Principal Investigator	R09	30	1	5	3.75	1.25	$335.28	$0.01
	R10	200	10	1	0.75	0.25	$67.06	$0.13
	R11	200	5	8	6.00	2.00	$536.45	$0.54
Total								$5.8

Note: * Hourly median wage rate for sponsor, QAU, and management with executive responsibility is $105.60, $79.80 for contributing scientists or principal investigators, and $28.84 for clerical assistants. Total may not add up due to rounding. See Table 4A for a description of each reporting code. The number of affected entities and additional burden come from the Paperwork Reduction Act estimates in the preamble.

4. Recordkeeping Costs

The proposed rule proposes additional recordkeeping responsibilities from multiple entities involved in the conduct of a nonclinical laboratory study to enhance the information that is essential for appropriate conduct of nonclinical laboratory studies, e.g., documenting protocol and SOPs approval, documenting training and inspectional findings. Table 4C below briefly describes the additional proposed recordkeeping requirements, and the proposed entity responsible for ensuring each of the additional requirements is fulfilled.

Table 4C.--Additional Recordkeeping Responsibilities Proposed by Rule

Main Entity Responsible*	Additional Documentation Responsibility
Sponsor	K01. Protocol approval, including all amendments
	K02. Animal welfare determination
	K03. Accreditation status of person conducting the animal testing
	K04. Test, control, and reference article parameters
	K05. Archival locations
	K06. Qualifications of contracted persons
Management with executive responsibility	K07. Training and experience on GLP
	K08. Training and experience on animal care
	K09. All persons are qualified for multisite studies
	K10. Periodic review of GLP Quality System
	K11. Periodic review of QAU
	K12. Appointment of management representative
	K13. All test sites have master schedule
	K14. Appointment of person to manage master schedule
	K15. Selection of lead QAU for multisite studies
Quality Assurance Unit (QAU)	K16. Process-based inspections
	K17. Audits of final reports of contributing scientists
	K18. Audits of principal investigator reports
	K19. Audits of final study reports for multisite studies
	K20. Review of protocols and amendments
	K21. Review of SOPs and amendments as they pertain to specific studies
Study Director	K22. Multisite need for PIs
	K23. Document communications
	K24. Compliance with protocol

	K25. QAU review of protocol and applicable SOPs
	K26. Management provided adequate resources
	K27. Computerized systems validated
	K28. Review by animal study review board
	K29. Multisite personnel qualified
	K30. Test system as required
	K31. GLP compliance
	K32. Test article accountability when containers disposed of
Independent Contributing Scientist	K33. Education, training, and experience
	K34. Archive location
	K35. Appropriate animal care (when applicable)
Principal Investigator	K36. Protocol and protocol amendment acceptance
	K37. Study deviations
	K38. Archive location

Note: * Task may involve other assistance such as clerical.

To estimate recordkeeping costs we use the same wage rates discussed in section E1 above. However, we assume that documentation and recordkeeping activities involve 75 percent of the total labor hours allocated to clerical assistants and 25 percent to the main entity responsible for the documentation. Thus, after adjusting for benefits and overhead, the hourly wage rate for entities with a managerial role ("Management Occupations," SOC 110000) is $105.60 and $28.84 for clerks ("File Clerks," SOC 434071).

Estimated total cost for each of the additional recordkeeping responsibilities is determined by multiplying the number of entities affected by the annual recordkeeping frequency per entity affected and the unit labor cost (for brevity we provide this information in Appendix Table A1). Unit cost of labor for each recordkeeping responsibility is calculated as the labor hours per entity involved in the specific task times the wage rate. For instance, total cost of $10.53 million for responsibility K01, "Protocol approval, including all amendments", is calculated as follows: 2,193 respondents x 100 responses per respondent x (0.25 hours x $105.60 per hour + 0.75 hours x $28.84 per hour). The recordkeeping costs for the remaining

responsibilities, K02-K38, are calculated following the same approach. We expect that the average number records for recordkeeping of protocol approval, including all amendments, may vary across, and within, industries and seek comments supported by data.

Table 4D below provides a summary of the recordkeeping costs by the main entity responsible. Total estimated annual cost is $27.6 million. Again, even though the proposed recordkeeping responsibilities would be required from entities other than the sponsor, all costs are assumed to be ultimately borne by the sponsor funding the nonclinical laboratory study.

Table 4D.--Estimated Annual Recordkeeping Cost

Main Entity Responsible*	Cost Item Codes	Estimated Cost ($million)
Sponsor	K01-K06	$13.75
Management with executive responsibility	K07-K15	$1.93
Quality Assurance Unit (QAU)	K16-K21	$6.36
Study Director	K22-K32	$5.41
Independent Contributing Scientist	K33-K35	$0.00
Principal Investigator	K36-K38	$0.14
Total		$27.60

Note: See Appendix Table A1 for further details on costs per item.

5. One-Time Costs from Reading and Understanding

We estimate the one-time costs to read and understand the proposed rule would be between $1.49 million and $2.98 million, or $2.24 million on average. To calculate this cost, we first estimate the time to read and understand the proposed rule (Table 4E). Then, we estimate the cost for entities that would face lower complexity from reading the proposed rule and for entities that would face higher complexity (Table 4F).

Table 4E.--Time to Read and Understand the Proposed Rule (per Entity)

Lower Bound	**Low Complexity**	**High Complexity**
Words of preamble	36,000	36,000
Words read per minute	250	200
Hours to read	2.4	3.0
People to read	1	2
Total hours to read	2.4	6.0
Total hours to understand	2.4	6.0
Total hours to read and understand	**4.8**	**12.0**
Upper Bound	**Low Complexity**	**High Complexity**
Words of preamble	36,000	36,000
Words read per minute	250	200
Hours to read	2.4	3.0
People to read	2	4
Total hours to read	4.8	12.0
Total hours to understand	4.8	12.0
Total hours to read and understand	**9.6**	**24.0**

Note: The number of words is an approximation and includes title and other words that some entities would potentially skip. Therefore, such count is an upper bound of the reading burden.

In Table 4E we calculate lower and upper estimates of time to read and understand the proposed rule under a low-complexity scenario for sponsors of nonclinical laboratory studies who would face fewer provisions. Our estimates under a high-complexity scenario apply to entities that would have to read and understand more provisions in the rule. Each calculation, under either scenario, multiplies the estimated words in the preamble by the reading speed and by the number of people to read and understand the rule. We use the resulting estimates in Table 4F to calculate the monetary cost.

Table 4F.--Cost to Read and Understand the Proposed Rule ($ Dollars)

Lower Complexity	**Low**	**High**	**Average**
Number of firms	2,193	2,193	
Hours to read and understand	4.8	9.6	
Adjusted hourly wage	$105.6	$105.6	
Cost per firm	$506.9	$1,013.8	
Cost to read and understand the rule	$1,111,588	$2,223,176	**$1,667,382**
Annualized over 10 years 3%			$195,468
Annualized over 10 years 7%			$237,398
Higher Complexity	**Low**	**High**	**Average**
Number of firms	300	300	
Hours to read and understand	12.0	24.0	
Adjusted hourly wage	$105.6	$105.6	
Cost per firm	$1,267.2	$2,534.4	
Cost to read and understand the rule	$380,160	$760,320	**$570,240**
Annualized over 10 years 3%			$66,850
Annualized over 10 years 7%			$81,189
Total costs to read and understand	**$1,491,748**	**$2,983,496**	**$2,237,622**

Note: The number of entities is from the Paper Reduction Act analysis in the preamble of this proposed rule.

In Table 4F, we calculate the cost to read and understand the proposed rule for two groups of entities. The first group at the top of the table is for sponsors of nonclinical laboratory studies; the second group at the bottom half of the table represents estimates for testing facilities of nonclinical laboratory studies. For example, for the first group, multiplying the number of entities (2,193) by our estimates of hours to read and understand (4.8 hours, from Table 4E) by hourly wage adjusted for benefits and overhead ($105.6), results in $1.1 million as the lower bound. After estimating lower and upper estimates for each group of entities, we then add costs for the two groups to calculate total costs at the bottom of the table, which range from $1.49

million to $2.98 million, or $2.24 million on average. In addition to total costs, we also present costs per firm and annualized costs over a 10-year period.

6. One-Time Costs from Updating SOPs and Writing New SOPs

We estimate the one-time costs to update existing SOPs and to write new SOPs combined would range between $5.1 million to nearly $12 million, or around $8.6 million on average. For example, Table 4G shows that to calculate the cost of updating SOPs, we multiply the number of SOPs per entity (12) by the time estimate to update an SOP (4 hours) by the adjusted hourly wage ($86.4) and by the number of entities (300), thus resulting in a lower bound estimate of $1.2 million. We estimate the rest of the estimates in the same way. The 300 firms represent independent testing laboratories that firms regulated by any of our centers may contract out to perform nonclinical laboratory studies on their behalf.

Table 4G.--Cost to Update Existing SOPs and to Write New SOPs ($ Dollars)

Update Existing SOPs	**Low**	**High**	**Average**
Number of SOPs to update (per entity)	12	12	
Time to update existing SOPs (hours)	**4**	**11**	
Adjusted hourly wage	$86.4	$86.4	
Cost per firm	$4,147.68	$11,406.12	
Number firms	300	300	
Total cost to update SOPs	$1,244,304	$3,421,836	
Write New SOPs	**Low**	**High**	**Average**
Number of SOPs to write (per entity)	10	10	
Hours to write new SOPs (hours)	**15**	**33**	
Adjusted hourly wage	$86.4	$86.4	
Cost per firm	$12,961.5	$28,515.3	
Number firms	300	300	
Total cost to write new SOPs	$3,888,450	$8,554,590	
Total one-time cost to update existing SOPs and to write new	$5,132,754	$11,976,426	**$8,554,590**

SOPs			
Annualized over 10 years 3%			$1,002,859
Annualized over 10 years 7%			$1,217,981

Note: Part 58.81 describes the SOP provisions, and based on such provisions we estimate testing facilities would update 12 SOPs each and write 10 additional SOPs. We use a 2007 ERG report (Evaluation of Recordkeeping Costs for Food Manufacturers) to account for the number of hours that would be required to fulfill each SOP provision. The adjusted hourly wage assumes that managerial staff would participate in 75% of the process and that the remaining 25% of the process would be completed by clerical staff. Thus, the adjusted hourly wage is: 0.75 x $105.6 + 0.25 x $28.82. This adjusted wage also reflects adjustments for overhead.

7. One-Time Costs from Training

We estimate the one-time costs for training would be between $0.3 million and $2.9 million, or $1.6 million on average. To calculate this cost, we consider that for the low estimate one person would be doing the training and one person would be trained. By contrast, for the high estimate we consider that also one person would be doing the training and potentially three people would receive such training. We then multiply the number of people involved in each case by the number of hours and by the adjusted (for overhead and benefits) wage value and by the number of entities.

Table 4H.--Cost for Training ($ dollars)

Initial Training	**Low**	**High**	**Average**
Number of employees in training (per entity)	2	4	
Time to train (hours)	**5**	**23**	
Adjusted hourly wage	$105.6	$105.6	
Cost per firm	$1,056.00	$9,715.20	
Number firms	300	300	
Total cost to update SOPs	$316,800	$2,914,560	**$1,615,680**
Annualized over 10 years 3%			$189,407
Annualized over 10 years 7%			$230,036

Note: We use a 2007 ERG report (Evaluation of Recordkeeping Costs for Food Manufacturers) to account for the number of hours that would be required for training.

8. Summary of Costs

The estimated reporting, recordkeeping, reading and understanding, SOP, and training costs are summarized in Table 4I below. The first half of this table shows the one-time costs,

which annualized at 7-percent over a 10-year period would range from $1 million to $2.5 million, or $1.8 million on average. In the second half of the table, costs are annual, and we do not need to annualize such estimates. These annual costs of reporting and recordkeeping combined would range from $33.4 million to $66.8 million and average $50.1 million. Combined, the annualized total costs, at 7% over a ten-year period, would range from $34.4 million to $69.3 million and would average $51.9 million. Using a 3-percent discounting rate, total annualized costs would range from $34.2 million to $68.9 million and would average $51.5 million.

If approximately 2,193 sponsors would be affected by the proposed rule, the average (rounded off) annualized cost per sponsor would be between $15,678 ($34.4 million divided 2,193 sponsors) and $31,617 ($69.3 million divided by 2,193 sponsors) with a 7 percent discount rate, or between $15,599 ($34.2 million divided by 2,193 sponsors) and $31,412 ($68.9 million divided by 2,193 sponsors) with a 3 percent discount rate. This simple calculation assumes that sponsors ultimately bear the cost that would arise from the proposed rule. Although the number of sponsors comes from the Paperwork Reduction Act estimate, included in the preamble of this proposed rule, we seek comments or data to support other estimates presented here or elsewhere in this analysis.

Table 4I.--Total Costs of the Proposed Rule ($ Millions)

Type of cost	**Frequency**	**Low**	**High**	**Average**
Read and understand	one-time	$1.5	$3.0	$2.2
SOP update and write	one-time	$5.1	$12.0	$8.6
Training	one-time	$0.3	$2.9	$1.6
Total one-time		$6.9	$17.9	$12.4
Total one-time annualized 7%		$1.0	$2.5	$1.8
Total one-time annualized 3%		$0.8	$2.1	$1.5
Reporting	Annual	$5.8	$11.6	$8.7
Recordkeeping	Annual	$27.6	$55.2	$41.4

Total annual		$33.4	$66.8	$50.1
Total Annualized 7%		**$34.4**	**$69.3**	**$51.9**
Total Annualized 3%		**$34.2**	**$68.9**	**$51.5**

Note: In the first half of the table costs are annualized over a ten year period. For the second half, costs are annual, and we do not need to annualize such estimates. Totals may not add up due to rounding.

Under the proposed regulation, any person conducting one or more phases of a nonclinical laboratory study would be subject to inspection and disqualification. The implied assumption made throughout this analysis is that there will be 100 percent compliance, and as such inspection and disqualification costs were not included in our estimates. We also assume that resources to conduct additional compliance and enforcement are held constant—either there is no change in our budget to these activities, or there is no reallocation of existing resources from other areas. Relaxing these assumptions might increase the costs of the proposed rule for industry. We may have inadvertently excluded some potential costs of the proposed rule and welcome comments from affected laboratories. We also request detailed comment on our cost estimate from academic and any other affected entities conducting nonclinical laboratory studies intended to support an application or submission.

G. Analysis of Regulatory Alternatives to the Proposed Rule

1. No Change in Regulation

The simplest alternative would be to leave the existing GLP regulation unchanged. Under the current regulation, failure to specifically include all persons conducting a phase of a multisite study would remain unchanged and gaps in the current quality system would remain unaddressed. Without addressing such gaps, the quality and integrity of the data used to support an application or submission to us might be suboptimal. Additionally, any inefficient use of

resources to comply with regulations that differ from international standards or current practices would continue.

2. Publish Additional Guidance

While guidance exists with respect to GLP regulation (Ref. 4), without regulation that explicitly delineates the roles and responsibilities of the organizational structure and personnel, study misconduct may continue along the observed increasing trend. FDA's GLP guidance document represents our recommendations with regard to the conduct of GLP studies, but it does not establish legally enforceable responsibilities. Therefore, under this alternative, if the recommendations in the guidance are not followed, the proposed benefits from improved international consistency and improved data integrity and quality will not be realized.

H. International Effects

Foreign entities that are proposed to be subject to the proposed rule would incur the same costs associated with the preparation and submission of the proposed requirements as incurred by firms operating in the United States. The proposed rule would be unlikely to alter the current mix of foreign and domestic manufacturing for the affected products. Nevertheless, we request comment on the impact of the proposed rule on foreign laboratories.

II. Initial Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to prepare an initial regulatory flexibility analysis if a proposed rule would have a significant effect on a substantial number of small businesses, non-profit organizations, local jurisdictions or other entities. This analysis, together with other relevant sections of this document, serves as the initial regulatory flexibility analysis required by the Regulatory Flexibility Act.

We find that there would be a substantial impact on firms employing fewer than 10 workers in "Dental Equipment and Supplies." We estimate an impact between 1.87 percent and 8.9 percent of average annual sales. Therefore, we anticipate that this rule may have a significant economic impact on some small entities, and invite comments from stakeholders on this conclusion. We also seek comment, particularly from small entities, about the proposed effective date of 1 year after the date of publication of any final rule that may issue to help us determine if such time frame is appropriate.[2]

A. Who is Affected

There are various types of entities that conduct nonclinical laboratory studies intended to support an application or submission. The nature of such entities may vary from general academic laboratories to specialized industry laboratories. Although some entities performing such nonclinical laboratory studies may be considered small according to the Small Business Administration (SBA), costs are likely paid by the sponsors funding the nonclinical laboratory studies which may be larger according to annual revenue.

The SBA uses different definitions of small entity for different industries. Table 5A below summarizes the size standards to determine a small business entity based on the SBA

[2] See the proposed rule, section VI. – Proposed Implementation Plan.

standards and the North American Industrial Classification System (NAICS) for the industries covered by the proposed rule (Proposed Rule Economics Ref. 5). Based on SBA size standards, except for blood and organ banks whose size is determined based on revenues, most firms covered by the proposed rule would be considered small if they employ fewer than 500 employees. Firms in the tobacco industry would be considered small if they employ fewer than 1,000 employees. Firms in the pharmaceutical industry are considered small if they employ fewer than 750 employees. Blood and organ banks would be considered small if their annual revenue is less than $10 million. Table 5A below provides a summary of the size standards as determined by the SBA.

We may have inadvertently excluded some potential entities such as academic laboratories because the NAICS classification does not allow disaggregation of such entities and because such entities likely perform other research beyond nonclinical laboratory studies. We request detailed comment on how the proposed rule would affect academic and any other entities conducting nonclinical laboratory studies intended to support an application or submission.

Table 5A.--Small Business Size Standards for Industries Covered by the Proposed Rule

NAICS Code or Subsector	Description	Size Standards (million$)	Size standards (Number of Employees)
311	Food Manufacturing (includes animal food)		500 to 1,000
3122	Tobacco Manufacturing		1,000
325412	Pharmaceutical preparation manufacturing		750
325413	In-vitro diagnostic substance		500
325414	Biological Product (except Diagnostic) Manufacturing		500
334510	Electromedical and electrotherapeutic		500
334516	Analytical laboratory instruments		500
334517	Irradiation apparatus		500
339112	Surgical and medical instruments		500
339113	Surgical appliance and supplies		500
339114	Dental equipment and supplies		500

339115	Ophthalmic goods		500
621991	Blood and Organ Banks	$10.00	

Currently available data from the 2007 Economic Census (Ref. 6) show that at least 92 percent of the establishments in pharmaceutical, medical devices, foods, and biologics (except blood and blood organs) industries would be considered small by SBA standards.[3] Our Registration and Listing data indicate that 15 (12.7 percent) of the registered tobacco manufacturers are considered small. Using revenue measures as determined by the SBA standards we estimate that 72 percent of blood and organ banks would be considered small (see table 5B).

Table 5B.--Estimated Number of Firms or Establishments Considered Small

NAICS Code or Subsector	Description	Total Number of Establishments	Establishments Considered Small*	Estimated Percent of Establishments or Firms Considered Small**
311	Food Manufacturing (includes animal food)***	25,616	25,019 – 25,443	97.7 - 99.3%
3122	Tobacco Manufacturing****	193	25	12.71%
325412	Pharmaceutical preparation manufacturing***	991	916-969	92.4 - 97.8%
325413	In-vitro diagnostic substance	259	245	94.6%
325414	Biological Product (except Diagnostic) Manufacturing	350	335	95.7%
334510	Electromedical and electrotherapeutic	671	638	95.1%
334516	Analytical laboratory instruments	636	620	97.5%
334517	Irradiation apparatus	181	175	96.7%

[3] Although the SBA standard indicates that a firm in NAICS 325412 would be considered small if it employs fewer than 750 employees, due to data limitations our estimate is based on the average number of establishments with 500 and 1000 employees.

339112	Surgical and medical instruments	1,340	1,293	96.5%
339113	Surgical appliance and supplies	2,219	2,189	98.6%
339114	Dental equipment and supplies	756	753	99.6%
339115	Ophthalmic goods	622	614	98.7%
621991	Blood and Organ Banks	1,267	908	72%

Note: *Due to the construction of the Economic Census data we are unable to disaggregate the data for establishments with fewer than 750 employees. ** NAICS 621991 includes 1267 establishments associated with 365 firms. To calculate the average annual sales we divide annual revenue by the total establishments in various employment size categories; a firm is considered small if its average sales are under $10 million. *** For NAICS code 325412 and subsector 311, the lower bound is based on the number of establishments with fewer than 500 employees, and the upper bound is based on the number of establishments with fewer than 1000 employees. **** Number of establishments for tobacco products is based on FDA registration and listing information, revenue data are from the 2007 Economic Census.

B. Economic Impact on Small Entities

The implementation of the proposed GLP Quality System will result in additional costs incurred by entities involved in the conduct of nonclinical laboratory studies, including the sponsor, testing facility, and any contracted persons. However, although costs are incurred by these various entities, the additional costs are ultimately paid by the sponsors funding the nonclinical laboratory studies. Thus, reducing or increasing the costs to any of these entities participating in the conduct of a nonclinical laboratory study will result in costs or savings realized by the sponsor. In the cost section, we estimate that the average annualized cost per sponsor is between $15,679 and $31,617 with a 7 percent discount rate. Using U.S. Census Bureau data on the average annual revenue for each industry or sector, we estimate the average annualized cost per sponsor as a percent of their average revenue for each of the affected industries (Table 5C). For example, the low estimate impact for small establishments in sector 311 is 0.098%, calculated as average annualized cost ($15,679) divided by average annual revenue ($15,938,000). Similarly, the high estimate impact for small establishments in sector 311

is 0.213%, calculated as $31, 617 divided by $15,938,000. All other calculations in the table follow the same steps using the respective average annual revenue but using the same costs estimates per sponsor.

Table 5C.--Estimated Economic Impact of the Proposed Rule on Small Entities

NAICS or Sector	Small Establishment				Large Establishment			
	Average Revenue ($1,000)	Unit Cost as a Percent of Average Revenue			Average Revenue ($1,000)	Unit Cost as a Percent of Average Revenue		
		Low	High	Average		Low	High	Average
311	$15,938	0.098%	0.198%	0.148%	$319,898	0.005%	0.010%	0.007%
3122*	$11,318	0.138%	0.279%	0.209%	$3,916,971	0.000%	0.001%	0.001%
325412	$60,962	0.026%	0.052%	0.039%	$1,160,470	0.001%	0.003%	0.002%
325413	$25,639	0.061%	0.123%	0.092%	$437,588	0.004%	0.007%	0.005%
325414	$20,634	0.076%	0.153%	0.114%	$992,395	0.002%	0.003%	0.002%
334510	$17,559	0.089%	0.180%	0.134%	$405,399	0.004%	0.008%	0.006%
334516	$13,448	0.116%	0.235%	0.176%	$277,881	0.006%	0.011%	0.008%
334517	$16,523	0.094%	0.191%	0.143%	$468,385	0.003%	0.007%	0.005%
339112	$12,456	0.125%	0.254%	0.190%	$293,519	0.005%	0.011%	0.008%
339113	$7,720	0.202%	0.410%	0.306%	$574,904	0.003%	0.005%	0.004%
339114	$5,182	0.301%	0.610%	0.456%	$241,505	0.006%	0.013%	0.010%
339115	$4,828	0.323%	0.655%	0.489%	$331,194	0.005%	0.010%	0.007%
621991	$5,273	0.296%	0.600%	0.448%	$11,492	0.136%	0.275%	0.205%

Note: *The Economic Census 2007 does not report data for establishments with fewer than 750 employees, therefore for all establishments, except those in NAICS code 621991, we define a business entity as small if it employs fewer than 500 employees. ** Except for NAICS 621991, average revenue is defined as the total value of shipments divided by the total number of establishments. For NAICS 621991, average revenue is total revenue divided by total number of establishments. *** Due to confidentiality, the Economic Census 2007 does not report the value of shipments for all firms in NAICS code 3122; thus, the average revenue for both small and large establishments is underestimated. To calculate the average annual sales we divide annual revenue by the total establishments in various employment size categories; an establishment is considered small if its average sales are under $10 million. Table 5A describes each NAICS category.

Based on the available data, we estimate that the average annualized cost per sponsor would represent a small portion of a typical sponsor's average annual revenue. Table 5C shows that the estimated cost would represent less than 1 percent of average annual sales for small establishments. This suggests that the proposed rule would not have a significant effect on a substantial number of small entities. We request detailed comment on our cost estimate from

academic and any other affected entities conducting nonclinical laboratory studies intended to support an application or submission.

We also examine whether there could be a disproportionate effect among some very small entities.[4] Table 5D shows that for entities in the "Dental Equipment and Supplies" industry (NAICS 339114), the proposed rule would have a greater impact on small entities employing fewer than 10 employees than on small entities employing more than 10 employees. The economic burden ranges between 1.87 percent and 8.94 percent of average annual sales for the very small entities with less than 10 employees, compared to 0.04 percent or less for entities employing between 100 and 499 workers. Moreover, the Census data indicate that small entities hiring fewer than 10 workers represent approximately 72 percent ((426+120)/756) of all establishments classified in this category. However, some very small entities included in the Census data may not be sponsors affected by the proposed rule, and some of the smallest sponsors may incur lower costs than the estimated average costs for all sponsors. Consequently, we request comment from very small sponsors about the expected burden of the proposed rule.

Table 5D.--Economic Impact on Establishments on Dental Equipment and Supplies (NAICS 339114)

Employees	Average Value of Shipments ($1,000)	Number of Establishments	Unit Cost as a Percent of Average Revenue		
			Low	High	Average
0-4	$353	426	4.41%	8.94%	6.68%
5-9	$834	120	1.87%	3.79%	2.83%
10-19	$1,753	75	0.89%	1.80%	1.35%
20-49	$5,467	72	0.29%	0.58%	0.43%
50-99	$17,888	28	0.09%	0.18%	0.13%
100-249	$78,583	25	0.02%	0.04%	0.03%
250-499	$94,425	7	0.02%	0.03%	0.03%

[4] Small Business Administration, "A Guide for Government Agencies: How to Comply with the Regulatory Flexibility Act," June 2010. http://www.sba.gov/sites/default/files/rfaguide.pdf, accessed November 6, 2015.

Note: Totals may not add up due to rounding.

III. References

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2. Organisation for Economic Co-operation and Development (OECD), http://www.oecd.org/chemicalsafety/testing/goodlaboratorypracticeglp.htm, accessed November 2015.

3. U.S. Bureau of Labor Statistics. "May 2014 National Occupational Employment and Wage Estimates," May 2014 Occupational Employment Statistics, http://data.bls.gov/oes/, accessed November 2015.

4. U.S. Food and Drug Administration. "Guidance for Industry. Good Laboratory Practices. Questions and Answers," July 2007, http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133748.pdf, accessed November 2015.

5. U.S. Small Business Administration. "Table of Small Business Size Standards Matched to North American Industry Classification System Codes," March 26, 2012. http://www.sba.gov/sites/default/files/files/Size_Standards_Table.pdf, accessed November 2015.

6. U.S. Census Bureau, "Industry Statistics for Subsectors and Industries by Employment Size: 2007 Economic Census," American FactFinder, data downloaded December 11, 2012, http://factfinder2.census.gov/, accessed November 2015.

7. Eastern Research Group, Inc., "Evaluation of Recordkeeping Costs for Food Manufacturers," pp. 62, 2007.

IV. Appendix

Appendix Table A1. Additional Recordkeeping Responsibilities Proposed by Rule

Main Entity Responsible*	Additional Documentation Responsibility	Number of Entities Affected	Average Annual Records	Labor Hours (per response)			Unit Cost	Total Cost ($mil)
				Total Hours per Response	Main Entity	Clerical Assistant		
Sponsor	K01. Protocol approval, including all amendments	2,193	100	1.0	0.25	0.75	$48.03	$10.53
	K02. Animal welfare determination	1,316	5	2.0	0.50	1.50	$96.06	$0.63
	K03. Accreditation of person conducting the animal testing	1,316	5	0.5	0.13	0.38	$24.02	$0.16
	K04. Test, control, and reference article parameters	1,316	5	0.5	0.13	0.38	$24.02	$0.16
	K05. Archival locations	2,193	62	0.3	0.06	0.19	$12.01	$1.64
	K06. Qualifications of contracted persons	1,316	5	2.0	0.50	1.50	$96.06	$0.63
Management with executive responsibility	K07. Training and experience on GLP	300	5	0.3	0.06	0.19	$12.01	$0.02
	K08. Training and experience on animal care	300	500	0.3	0.06	0.19	$12.01	$1.80
	K09. All persons are qualified for multisite studies	300	0.25	0.5	0.13	0.38	$24.02	$0.00
	K10. Periodic review of GLP Quality System	300	1	0.5	0.13	0.38	$24.02	$0.00
	K11. Periodic review of QAU	300	0.1	0.3	0.06	0.19	$12.01	$0.00
	K12. Appointment of management representative	300	15	0.3	0.06	0.19	$12.01	$0.05
	K13. All test sites have master schedule	300	0	1.0	0.25	0.75	$48.03	$0.00
	K14. Appointment of person to manage master schedule	300	5	0.5	0.13	0.38	$24.02	$0.04
	K15. Selection of lead QAU for multisite studies	300	5	0.3	0.06	0.19	$12.01	$0.02
Quality Assurance Unit (QAU)	K16. Process-based inspections	150	5	0.3	0.06	0.19	$12.01	$0.01
	K17. Audits of final reports of contributing scientists	300	600	0.5	0.13	0.38	$24.02	$4.32
	K18. Audits of principal investigator reports	300	120	0.5	0.13	0.38	$24.02	$0.86

	K19. Audits of final study reports for multisite studies	300	60	0.5	0.13	0.38	$24.02	$0.43
	K20. Review of protocols and amendments	300	17	1.5	0.38	1.13	$72.05	$0.37
	K21. Review of SOPs and amendments as they pertain to specific studies	300	17	1.5	0.38	1.13	$72.05	$0.37
Study Director	K22. Multisite need for PIs	300	180	1.0	0.25	0.75	$48.03	$3.07
	K23. Document communications	300	180	0.3	0.06	0.19	$12.01	$0.77
	K24. Compliance with protocol	300	60	1.0	0.25	0.75	$48.03	$0.87
	K25. QAU review of protocol & SOPs	300	17	0.3	0.06	0.19	$12.01	$0.06
	K26. Management provided adequate resources	300	5	0.5	0.13	0.38	$24.02	$0.04
	K27. Computerized systems validated	300	5	0.3	0.06	0.19	$12.01	$0.02
	K28. Review by animal review board	300	17	0.3	0.06	0.19	$12.01	$0.06
	K29. Multisite personnel qualified	300	15	1.0	0.25	0.75	$48.03	$0.22
	K30. Test system as required	300	5	0.3	0.06	0.19	$12.01	$0.02
	K31. GLP compliance	300	60	1.0	0.25	0.75	$48.03	$0.87
	K32. Test article accountability when containers disposed of	300	6	0.3	0.06	0.19	$12.01	$0.02
Independent Contributing Scientist	K33. Education, training, and experience	30	1	0.3	0.06	0.19	$10.39	$0.00
	K34. Archive location	30	1	0.3	0.06	0.19	$10.39	$0.00
	K35. Appropriate animal care (when applicable)	2	1	0.5	0.13	0.38	$20.79	$0.00
Principal Investigator	K36. Protocol and protocol amendment acceptance	200	5	0.3	0.06	0.19	$10.39	$0.01
	K37. Study deviations	200	10	0.5	0.13	0.38	$20.79	$0.04
	K38. Archive location	200	40	0.3	0.06	0.19	$10.39	$0.08
Total								$27.6

Note: * Task may involve other assistance such as clerical. Hourly median wage rate for sponsor, QAU, and management with executive responsibility is $105.60, $79.80 for contributing scientists or principal investigators, and $28.84 for clerical assistants. Total may not add up due to rounding.