DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic

Docket No. FDA-2019-N-2650

Preliminary Economic Analysis of Impacts:
Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
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Executive Summary

Quantifiable benefits of this proposed rule are cost savings that come from reducing the burden of submitting investigational new drug applications (INDs) to the Food and Drug Administration (FDA) for clinical investigations to evaluate a drug use of a product that is lawfully marketed as a food for human consumption (including both conventional foods and dietary supplements) or as a cosmetic. The proposed rule would have a one-time, upfront cost for current and future sponsors and sponsor-investigators who would have to read the rule. In addition, there would be costs to FDA associated with a new type of IND-related submission, a request for an FDA-determined exemption. The impact of this new submission is analyzed in section II.E, "Benefits of the Proposed Rule," as a partial offset to the cost savings of the rule. Discounted over 10 years, the total net benefit of the rule is estimated to be $33 million at a 3% discount rate and $27 million at a 7% discount rate.

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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 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would create net cost savings for the affected industry by reducing the number of investigational new drug applications (INDs) that must be submitted to the Food and Drug Administration (FDA or the Agency), we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before 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

Quantifiable benefits of this proposed rule are cost savings that come from reducing the burden of submitting INDs to FDA for clinical investigations evaluating drug uses of lawfully marketed foods for human consumption (including conventional foods and dietary supplements) and cosmetics. (We refer to these product categories collectively as "foods and cosmetics" or "CFSAN-regulated products" in this document). The cost savings would go to sponsors and sponsor-investigators (collectively, "sponsors"), typically physicians and other researchers at hospitals and academic institutions, who would no longer need to submit as many INDs because the proposed rule provides exemptions for qualifying drug studies of products lawfully marketed as a food or cosmetic. The proposed rule also would provide net cost savings to FDA, which would not need to evaluate and monitor as many INDs. We expect the average present value of the benefits to be $28 million at a 7% discount rate and $34 million at a 3% discount rate over a 10-year time horizon.

If this proposed rule is finalized, sponsors would incur a one-time cost because they, or lawyers or consultants acting on their behalf, would have to spend time reading the rule to understand which studies are eligible for an exemption and how to request an exemption. We estimate that 557 sponsors would read the rule the first year and 279 additional sponsors would read the rule in subsequent years. We estimate the cost of reading the rule to be $153 per sponsor. We expect the

average present value of the reading cost to be $418,000 at a 3% discount rate and $364,000 at a 7% discount rate over a 10-year time horizon. In addition, there would be costs to FDA associated with a new type of IND-related submission, a request for an FDA-determined exemption. The impact of this new submission is analyzed in section II.E, "Benefits of the Proposed Rule," as a partial offset to the cost savings of the rule. The total net benefit of the rule is estimated to be $33 million at a 3% discount rate and $27 million at a 7% discount rate.

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 $/year	$3,450,000	($850,000)	$7,730,000	2021	7%	10	Cost savings to FDA and industry
		$3,530,000	($780,000)	$7,840,000	2021	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $ /year	$45,300	$15,700	$77,800	2021	7%	10	
		$43,800	$15,100	$75,700	2021	3%	10	
	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: Small Business: Wages: Growth:							

We request comment on our estimates of the costs and benefits of this proposed rule.

II. Preliminary Regulatory Impact Analysis

A. Background

FDA is proposing to amend its regulations on INDs to exempt certain clinical investigations evaluating drug uses of foods and cosmetics from most IND requirements. Under the proposal, such clinical studies would not have to be conducted under an IND when, among other things, the study is not intended to support a drug development plan or marketing of the product for any drug use, and the study does not present a potential for significant risk to the health, safety, or welfare of subjects. Though exempt from most IND requirements, such investigations would still be subject to other regulations designed to protect the rights, safety, and welfare of subjects, such as requirements for informed consent and review by institutional review boards (IRBs).

Currently, FDA regulations provide an exemption from most IND requirements for studies of lawfully marketed drug products that meet certain criteria, including that the study does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of these risks) associated with the use of the drug product. However, this exemption applies only to clinical investigations of *drugs* lawfully marketed in the United States, and therefore generally does not apply to clinical investigations of products lawfully marketed as foods or cosmetics in the United States.

FDA has exercised its enforcement discretion on a case-by-case basis and has not objected to certain clinical studies evaluating a drug use of a product lawfully marketed as a food or cosmetic being conducted without an IND, based on consideration of factors such as the purpose of the investigation and whether the study raises any concerns about the health, safety, and welfare of subjects. The proposed rule would now establish exemptions from the IND requirements for drug studies of products lawfully marketed in the United States as a food or cosmetic when the studies meet criteria similar to those in the IND exemption for certain investigations of lawfully marketed drug products (21 CFR 312.2(b)(1)).

By exempting from the IND requirements certain low-risk studies evaluating drug uses of lawfully marketed foods and cosmetics, the proposed rule would reduce the regulatory burden of conducting such studies, without lessening protections for human subjects in studies that pose significant risks or jeopardizing the quality of data from studies used to support marketing approval for a drug or biological product.

B. Need for Federal Regulatory Action

The proposed rule would establish new IND exemptions for certain clinical investigations of products lawfully marketed as foods and cosmetics, similar to an exemption that already applies to some clinical investigations of drug products lawfully marketed in the United States. For many of these investigations, the proposed rule would make clear that the investigation is exempt from the IND requirements, without the sponsor having to ask FDA whether an IND is required. Thus, the proposed rule would address informational asymmetry by providing greater clarity and consistency to sponsors, investigators, and others about when a clinical study to evaluate a drug use of a food or cosmetic must be conducted under an IND.

By creating exemptions from the IND requirements for certain low-risk clinical studies evaluating a drug use of a food or cosmetic, the proposed rule would make it less time-consuming and costly for sponsors to conduct such studies. Without this rulemaking, sponsors may be unsure whether their clinical study must be conducted under an IND and spend more than the optimal amount of time submitting inquiries on the matter. The proposed rule would also reduce the time FDA employees need to spend responding to inquiries and evaluating and monitoring INDs.

C. Purpose of the Proposed Rule

The proposed rule would create two types of IND exemptions for clinical investigations to evaluate a drug use of products lawfully marketed in the United States as foods or cosmetics. One exemption, the proposed "self-determined exemption" (SDE), would specify that a clinical investigation to evaluate a drug use of a product that is lawfully marketed in the United States as a food or cosmetic is exempt from the IND requirements if certain conditions are met, including that the investigation is not intended to support a drug development plan for the product or a change in the labeling of the lawfully marketed product that would cause it to become an unlawfully marketed drug, and that the investigation meets certain criteria concerning the health, safety, and welfare of subjects.[1]

Under the proposed SDE, if a clinical investigation to evaluate a drug use of a product that is lawfully marketed in the United States as a food or cosmetic meets these criteria, the study would be exempt from most requirements in the IND regulations. Accordingly, the sponsor would not have to submit an IND for the study. In addition, the sponsor would not have to request that FDA exempt the study from the IND requirements.

Under the second proposed IND exemption, the "FDA-determined exemption" (FDE), the sponsor of a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a food or cosmetic could ask FDA to exempt the investigation from the IND requirements when the investigation meets the SDE criteria except for one or more of the subject health, safety, and welfare criteria, but the sponsor has concluded that the investigation nevertheless does not present a potential for significant risk to subjects.

To obtain such an exemption, the sponsor would submit a written request that includes the following: a copy of the study protocol or a detailed protocol summary with information about the study design, investigational product, and procedures; the names of the manufacturer and source of the product to be studied; the name (if different from the name of the product to be studied in the investigation) and form of the lawfully marketed food or cosmetic product, with a copy of the product's labeling and, if the labeling does not list the product's ingredients, a description of the product's composition; the source(s) of funding for the investigation; contact information for the sponsor; a brief description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of study subjects; and any other information requested by FDA.

Upon receiving such a request for exemption from the IND requirements, FDA would evaluate any risks to subjects and would grant an exemption if we found that the investigation did not

[1] See the proposed rule for a full list of conditions the investigation must meet to be exempt and the criteria that must be met concerning the health, safety, and welfare of the subjects.

present a potential for significant risk (or decrease the acceptability of the risks) to the health, safety, or welfare of subjects.

The proposed rule also would authorize FDA to grant an exemption from the IND requirements on our own initiative (i.e., the sponsor would not have to submit an FDE) if we determined, upon review of an IND, that the study met the decision criteria for an FDE.

D. Baseline Conditions

In some cases, sponsors may initiate or fund a study of a food or cosmetic for other uses (such as treating or preventing a disease) because the sponsor hopes to develop and obtain marketing approval of the product as a drug, has a financial relationship with an entity that hopes to obtain such marketing approval, or wishes to market the product for disease treatment or prevention without seeking approval for it as a new drug. In other cases, the motivation for conducting a study may be purely scientific or medical, and the sponsor may have no intent to seek approval of the product as a drug or to use the research results to market the product unlawfully for a drug use without such approval. Under current regulations, the great majority of clinical studies investigating drug uses of a food or cosmetic are not eligible for the IND exemption for which similar investigations of a lawfully marketed drug product are eligible.[2]

FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) receive about 4,170 INDs and 656 IND-related inquiries annually.[3] Of these, about 12 INDs and 58 inquiries (1.43% of the total inquiries and INDs received) concern clinical investigations of a product marketed as a food or cosmetic. Approximately 75% of these INDs and inquiries concern a drug use of a dietary supplement, 15% concern a drug use of a conventional food, and 4% concern a drug use of a cosmetic. The remaining submissions pertain to studies of conventional foods, dietary supplements, or cosmetics not intended for use as drugs and therefore are not covered by the proposed rule.

To help estimate the potential impact of establishing the IND exemptions proposed in this rule, FDA reviewed all INDs and IND inquiries received in 2016 through 2020 that concerned clinical investigations of products marketed as foods or cosmetics. In this time period, FDA received 75 such INDs and 247 such IND inquiries. Currently, FDA exercises enforcement discretion on a case-by-case basis with respect to IND requirements for some clinical studies evaluating drug uses of products lawfully marketed as foods or cosmetics, based on consideration of factors such as the purpose of the study and whether the study raises any concerns about the health, safety, or welfare of subjects. In these five years, FDA notified the sponsor of the Agency's intent to exercise enforcement discretion regarding approximately 40% of INDs and inquiries concerning clinical investigations of products marketed as foods or cosmetics. We incorporate this exercise of enforcement discretion within the baseline of this economic analysis (see Section J for further discussion of the impact of FDA's exercise of enforcement discretion).

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[2] See 21 CFR 312.2(b)(1) for the details of this exemption from the IND requirements.

[3] See Tables 1 and 4 in "Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Investigational New Drug Applications" (84 FR 3462; February 12, 2019).

About 15% of the INDs and IND inquiries involved studies that were determined not to require an IND, suggesting a lack of clarity about when the IND requirements apply to studies involving products marketed as food or cosmetics. FDA estimates that an inquiry concerning applicability of the IND requirements to a clinical investigation takes a sponsor about 24 hours to complete.[4] The average hourly wage of a person in the "Research and development in the physical, engineering, and life science" industry (NAICS 54171) is $57.38.[5] After applying the standard wage multiplier of two to account for employee benefits and other overhead costs, we estimate that submitting an inquiry to FDA costs a sponsor about $2,750 in the first year (= 24 hours*$114.76 hourly). There are no additional annual costs associated with the inquiry itself, but if the study is found to require an IND, the sponsor must submit an IND and comply with the annual reporting requirements in the IND regulations (see cost estimate in the following paragraph).

We estimate that preparing and submitting an IND that complies with the IND content and format requirements takes a sponsor approximately 1,600 hours per submission. The average time spent on IND annual reports is estimated at 360 hours per submission.[6] Using the same NAICS 54171 wage, we estimate that submitting an IND costs a sponsor about $183,600 in the first year (=1,600 hours*$114.76 hourly), and post-submission IND requirements like submitting adverse event reports and annual progress reports cost $41,300 annually (= 360 hours*$114.76 hourly) thereafter.

FDA staff read and evaluate each inquiry or IND for a clinical study to evaluate a possible drug use of a CFSAN-regulated product. Across the Agency, we estimate that reading and evaluating an average inquiry takes about 15 hours total, distributed among several FDA employees with differing roles and fields of expertise; reading and evaluating an IND for a study to evaluate a possible drug use of a CFSAN-regulated product takes two to four times as long, or 45 hours on average. An average FDA employee's hourly wage is $66.97. After applying the wage multiplier, we estimate that reading and reviewing an inquiry costs FDA $2,009 (=15 hours*$133.94 hourly) and reading and reviewing an IND costs FDA $6,027, on average (=45 hours*$133.94 hourly). In addition to the initial time spent reading and evaluating each inquiry or IND, FDA also reviews IND-related submissions, such as safety reports and annual progress reports. We do not include the time spent reading and reviewing these submissions because the nature of reviewing such submissions varies widely.

The 2017 Economic Census of the United States identifies approximately 15,000 establishments (also referred to as "entities" or "covered entities") in the "Research and development in the physical, engineering, and life science" industry.[7] The industry is broadly defined, comprising

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[4] FDA estimates the average burden per response for 21 CFR 312.2(e), "Requests for FDA advice on the applicability of part 312 to a planned clinical investigation," to be 24 hours (see 84 FR 3462, Tables 1 and 4).

[5] See U.S. Bureau of Labor Statistics, "May 2021 National Industry-Specific Occupational Employment and Wage Estimates: NAICS 541710 - Research and Development in the Physical, Engineering, and Life Sciences" at https://www.bls.gov/oes/current/naics5_541710.htm#00-0000.

[6] See 84 FR 3462, Tables 1 and 4.

[7] See TableID EC1700SIZEEMPFIRM, "ECN Core Statistics Economic Census: Establishment and Firm Size Statistics for the U.S.: Employment Size of Firms for the U.S.: 2017" at https://data.census.gov/cedsci/table?d=ECN%20Core%20Statistics%20Economic%20Census%3A%20Establishment%20and%20Firm%20Size%20Statistics%20for%20the%20U.S.&n=54171%3AN0500.00&tid=ECNSIZE2017.EC1700SIZEEMPFIRM .

establishments primarily engaged in conducting research and experimental development in the physical, engineering, and life sciences, such as agriculture, electronics, environmental science, biology, botany, biotechnology, computers, chemistry, food science, fisheries, forests, geology, health, mathematics, medicine, oceanography, pharmacy, physics, veterinary sciences, and other allied subjects. An example of an entity in this industry would be a university or independent laboratory conducting research in the physical, engineering, or life sciences. It is likely that not all entities categorized in this industry submit INDs or IND inquiries to FDA, let alone INDs or IND inquiries for clinical investigations evaluating a product marketed as a food or cosmetic. Given the small percentage of overall sponsor submissions (INDs and IND inquiries) for clinical investigations of food and cosmetics, we estimate that between 198 and 916 entities (1% to 5% of total entities) would be affected by this proposed rule.

E. Benefits of the Proposed Rule

Benefits of the proposed rule come in the form of cost savings to industry and FDA. Creating the proposed IND exemptions would reduce the burden of conducting certain clinical investigations evaluating drug uses of foods and cosmetics, as well as the Agency's burden of evaluating and monitoring such studies and reviewing IND inquiries, without eliminating requirements to help ensure the rights, safety, and welfare of study subjects and the quality of data submitted in support of drug product approval.

We estimate that submitting a request for an FDA-determined exemption (FDE) would take about the same amount of time as submitting an inquiry about whether the IND requirements apply, 24 hours. As with an inquiry, there would be no annual reporting or other additional annual costs associated with the FDE request. Thus, the initial sponsor cost per FDE request would be $2,750. We request comment on whether this under- or over-estimates the time and cost of submitting an FDE request.

The proposed rule would not require sponsors to submit anything to FDA in order to rely on the self-determined exemption (SDE). In addition, there would be no requirement for sponsors to keep records documenting that their study meets the criteria for this exemption. However, we recognize that other entities, such as the IRB with oversight over the clinical investigation, may require sponsors to keep records relating to the SDE. Therefore, because entities may choose to keep such additional records, which would increase the time-burden and thus the cost of an SDE, we estimate the initial time-burden to sponsors would be anywhere from 4 to 24 hours per exemption. Using the same wage rate described above, the initial sponsor cost for an SDE would be about $1,150, on average. We request comment on whether this under- or over-estimates the time and cost of keeping records to document that a study meets the criteria for the SDE.

Cost savings to sponsors can be estimated based on the difference between the baseline (current) cost of submitting an IND or IND-related inquiry regarding a clinical investigation (estimated in section D, "Baseline Conditions") and the cost of choosing one of the other options that would become available under the proposed rule (submitting a request for an FDE or self-determining that the clinical investigation is exempt under the proposed SDE). Table 2 shows the estimated cost savings by submission type. Based on our evaluation of the IND inquiries and INDs for clinical investigations of food and cosmetics reviewed between 2016 and 2020, we estimate that 25% of the investigations that were the subject of these previous inquiries and INDs would be eligible for an SDE, saving sponsors between $1,600 (for studies previously submitted as inquiries)

to $182,450 (for studies previously submitted as INDs) initially and $41,300 annually thereafter (for studies previously submitted as INDs). We estimate that under the proposed rule, approximately 15% of previous IND inquiries and INDs would be submitted as requests for an FDE, potentially saving sponsors $180,850 initially and $41,300 annually for studies previously submitted as INDs. FDA also anticipates that the proposed regulation will lead some sponsors who now submit IND inquiries to seek an FDE instead, and that an approximately equal number of other sponsors who now submit INDs will also request an FDE instead. Therefore, we estimate that the number of requests for an FDE will be 28 annually. We derived this estimate by doubling the number of IND inquiries and INDs for clinical investigations of food and cosmetics reviewed between 2016 and 2020 for which we would have granted an FDE.

A sponsor might choose to submit an IND instead of requesting an FDE because the sponsor is risk-averse: they would rather spend the additional time to prepare an IND than risk not having an IND for a clinical investigation that requires one. We expect that the rate at which this occurs will decrease over time as sponsors better understand the rule. If FDA grants an exemption from the IND requirements on its own initiative upon review of an IND, the sponsor would still incur the cost of submitting an IND, but would not incur annual reporting burdens thereafter. To the extent the Agency grants such exemptions, the cost savings of the rule are underestimated. We do not have enough data to quantify the effect of this FDA-initiated exemption.

If FDA denies a request for an FDE because the clinical investigation does not meet the proposed exemption criteria, the investigation would have to be conducted under an IND. We are uncertain what proportion of requests for an FDE would be denied; therefore, we do not include the additional cost a sponsor may incur to submit an IND and comply with the annual reporting requirements in the IND regulations *after* submitting an FDE for the same investigation. To the extent this occurs, the cost savings are overestimated.

We expect that the number of inquiries regarding applicability of the IND requirements will decrease by 5% each year due to increased clarity provided by the proposed rule; over a 10-year period, inquiries would decrease to 10% of IND-related submissions (INDs, IND inquiries, SDEs, and FDEs).

Table 2. Estimated Sponsor Cost Savings by Submission Type

Proposed Submission Type	Current Submission Type	Expected Total Submissions *(%)*	Sponsor Cost Savings Per Submission *($)*
SDE	Inquiry	20	Initial: 1,600 Annual: No change
SDE	IND	3	Initial: 182,450 Annual: 41,300
FDE	Inquiry	12	No change
FDE	IND	5	Initial: 180,850 Annual: 41,300
Inquiry	Inquiry	10	No change
IND	IND	50	No change

Notes: SDE is "Self-determined exemption" and FDE is "FDA-determined exemption."

Cost savings to FDA resulting from establishment of the proposed IND exemptions are calculated similarly and shown in Table 3. FDA's cost savings would be between $2,009 for each SDE previously submitted as an inquiry about the applicability of the IND regulations and $6,030 for an SDE previously submitted as an IND. We estimate that reviewing a request for an FDE will take us between 1.5 times and twice as long as a current inquiry review because review of an FDE request will likely involve more complex health, safety, and welfare issues than review of a typical inquiry now. We estimate that reviewing an FDE request would, on average, take 27 hours and cost FDA $3,616. Because of the longer review time, FDA would incur additional costs of $1,607 for this subset of total submissions. In an average year, this cost would be made up for in other cost savings. FDA's estimated cost savings would be $2,410 for each FDE previously submitted as an IND.

If FDA, after reviewing an IND, grants an FDE on its own initiative, we assume there is no cost savings to FDA because the reviewer still conducts the IND review and thus there is no change in cost savings per IND. However, FDA would experience reduced costs due to not having to review post-IND submissions, such as safety reports and annual progress reports, for such studies). As noted above, we do not attempt to quantify those cost savings because the time needed to read and review these submissions varies widely.

Table 3. Estimated FDA Cost Savings by Submission Type

Proposed Submission Type	Current Submission Type	Expected Total Submissions *(%)*	FDA Cost Savings Per Submission *($)*
SDE	Inquiry	20	2,009
SDE	IND	3	6,030
FDE	Inquiry	12	(1,607)
FDE	IND	5	2,410
Inquiry	Inquiry	10	No change
IND	IND	50	No change

Notes: SDE is "Self-determined exemption" and FDE is "FDA-determined exemption."

Table 4 summarizes the total cost savings to sponsors and FDA over ten years. The cost savings to sponsors estimated in Table 2 and the cost savings to FDA estimated in Table 3 are summed over the expected number of IND-related submissions each year. We assume that the total number of submissions FDA receives annually will remain the same as seen between 2016 and 2020, but will be distributed across the new types of submissions as shown in Table 2 and Table 3. Sponsors' annual cost savings will increase over 10 years as the number of expected annual IND progress reports and safety reports a sponsor would have had to submit if its investigation was subject to the IND requirements increases. About 99% of the proposed rule's total cost savings would be realized by sponsors.

Table 4. Average Sponsor and FDA Cost Savings over 10 years

Years after Effective Date	Sponsor	FDA
	$	*$*
1	1,850,000	36,000
2	2,280,000	37,000
3	2,690,000	38,000
4	3,110,000	39,000
5	3,610,000	39,000
6	4,100,000	40,000
7	4,600,000	41,000
8	5,100,000	42,000
9	5,590,000	43,000
10	6,090,000	43,000
Total	**39,020,000**	**397,000**

Present discounted values over a 10-year period are presented in Table 5. Discounted at 3%, the mean present value of cost savings of the proposed rule is $34 million, with a 90% confidence interval of negative 7.5 million to positive $75 million. Discounted at 7%, the mean present value of cost savings of the proposed rule is $28 million, with a 90% confidence interval of negative $6.8 million to $62 million. The range includes negative values, suggesting that it is possible there would be no cost savings given the variability over time in the number of SDE, FDE, inquiries, and IND submissions.

Table 5. Cost savings of Proposed Rule, in thousands, discounted over 10 years

Cost Savings (in thousands)	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	(7,470)	**33,620**	74,680
	7%	(6,780)	**27,650**	62,050
Annualized Value ($)	3%	(780)	**3,530**	7,840
	7%	(850)	**3,450**	7,730

F. Costs of the Proposed Rule

This proposed rule has a one-time upfront cost for current sponsors who would have to read and comprehend the rule to determine whether a study meets the requirements for a self-determined exemption or an FDA-determined exemption. In addition, there would be a cost in future years for new sponsors entering the field to read and comprehend the rule.

The cost of reading the rule is calculated using the time cost of a researcher at each covered entity. We expect between 198 and 916 covered entities will read the final rule in the first year after FDA publishes it, or an average of 557 covered entities. We anticipate about 279 (50% fewer) covered

entities will read the rule each year thereafter. The rule has about 16,000 words; the average reader can read 200 words per minute, so it should take about 1.33 hours to read. Using the hourly wage of $114.76 (including standard wage multiplier of 2 to cover benefits and overhead), the cost of reading the rule would be $153.01 per sponsor. Across all covered entities, the total cost of reading in the first year would be $85,200 (=$153.01/sponsor*557 covered entities) on average, with a low estimate of $30,300 (=$153.01/sponsor*198 covered entities) and a high estimate of $140,200 (=$153.01/ sponsor*916 covered entities). Annual reading costs for anticipated new sponsors would be $42,600 on average, estimated at half the first-year costs.

As noted above, entities may choose to keep additional records not required by the proposed rule, such as records required by the IRB with oversight over the clinical investigation. We request comment on any unintended costs or time-burdens that would offset the estimated cost savings to sponsors.

Relative to the baseline scenario described in Section D above, we do not expect a change in government administrative or enforcement costs associated with the proposed rule. Thus, there are no additional costs to FDA.

Present discounted values for the costs of the rule over a 10-year period are presented in Table 6. Discounted at 3%, the mean present value of costs of the proposed rule is $417,600, with a 90% confidence interval of $144,100 to $722,000. Discounted at 7%, the mean present value of costs of the proposed rule is $363,000, with a 90% confidence interval of $126,000 to $624,000.

Table 6. Costs of Proposed Rule, discounted over 10 years

Costs	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	144,100	**417,600**	721,600
	7%	126,100	**363,400**	624,400
Annualized Value ($)	3%	15,100	**43,800**	75,700
	7%	15,700	**45,300**	77,800

G. Distributional Effects

We do not expect there to be any distributional effects of this rule.

H. International Effects

We do not expect there to be any significant international effects of this rule. Foreign sponsors that currently submit INDs or inquiries about applicability of the IND requirements incur the same costs as sponsors in the United States. If a foreign sponsor submitted an IND or request for FDA-determined exemption, it would achieve the same cost savings as any domestic sponsor.

I. Uncertainty and Sensitivity Analysis

We account for uncertainty throughout the model and describe it in the "Benefits" and "Costs" sections above. The following data include ranges to account for uncertainty and variability in estimation: current and anticipated annual inquiry and IND submissions, sponsor cost of submitting inquiries and INDs, FDA cost of reviewing inquiries and INDs, FDA review time for the proposed FDE, and the number of affected entities.

The mean net benefits and a 90% confidence interval are described in Table 7.

Table 7. Net Benefits of Proposed Rule, in thousands, discounted over 10 years

Net Benefits in thousands	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	(7,610)	**33,200**	73,960
	7%	(6,910)	**27,290**	61,430
Annualized Value ($)	3%	(800)	**3,480**	7,760
	7%	(860)	**3,400**	7,660

It is possible that the proposed rule would not provide additional clarity for sponsors or investigators regarding applicability of the IND regulations to clinical investigations of foods or cosmetics. As a sensitivity analysis, we estimate net benefits assuming there are no changes in the number of inquiries, i.e., the anticipated 5% decrease in inquiries each year does not occur. The mean annualized net benefits discounted at 3% are roughly the same than in our main analysis, shown in Table 8.

Table 8. Sensitivity Analysis: Net Benefits of Proposed Rule, in thousands, discounted over 10 years

Sensitivity: Net Benefits in thousands	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	(7,890)	**33,050**	73,790
	7%	(7,140)	**27,170**	61,300
Annualized Value ($)	3%	(830)	**3,470**	7,740
	7%	(890)	**3,390**	7,640

J. Analysis of Regulatory Alternatives to the Proposed Rule

We analyze three regulatory alternatives to the proposed rule. In the first alternative, we assume that FDA decides not to make any changes to the current regulations and practices regarding clinical investigations of food or cosmetics. In this case, there would be no changes to the baseline estimated in Section D of this document.

The second regulatory alternative assumes that FDA does not make any changes to the current IND regulations and also does not exercise enforcement discretion with respect to IND requirements for any clinical investigations evaluating drug uses of foods or cosmetics. Under this Alternative 2, sponsors would have to submit more INDs and would therefore incur additional costs. FDA would also incur additional costs related to evaluating and monitoring these additional INDs. There would be no cost savings and thus the net benefits would be negative. Table 9 describes the net benefits under Alternative 2.

Table 9. Alternative 2: Net Benefits in thousands, discounted over 10 years

Alt. 2: Net Benefits in thousands	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	(47,570)	(93,600)	(139,400)
	7%	(38,940)	(77,320)	(115,520)
Annualized Value ($)	3%	(4,990)	(9,820)	(14,630)
	7%	(4,850)	(9,640)	(14,400)

Lastly, we estimate the net benefits if the proposed rule is modified to remove the sponsor-determined exemption (Alternative 3). Under this alternative, only the FDA-determined exemption would remain. Thus, sponsors would not be allowed to self-determine that their studies qualify for an exemption, and FDA would review each exemption request to determine whether the study met the exemption criteria. The mean net benefits discounted at 3% are positive and roughly equivalent to estimates in the main analysis. Table 10 describes the net benefits under Alternative 3.

Table 10. Alternative 3: Net Benefits in thousands, discounted over 10 years

Alt. 3: Net Benefits in thousands	Discount Rate	Low	**Primary**	High
Present Discounted Value ($)	3%	(8,380)	**32,590**	73,360
	7%	(7,570)	**26,760**	60,920
Annualized Value ($)	3%	(880)	**3,420**	7,700
	7%	(940)	**3,340**	7,590

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would create a net cost savings for the affected industry by reducing the number of INDs that must be submitted for clinical investigations evaluating drug uses of products lawfully marketed as foods or cosmetics, we propose to certify that the proposed rule will not 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

Entities affected by this proposed rule are classified in the "Research and development in the physical and life sciences" industry (NAICS 54171) by the Economic Census of Manufacturer.[8] This industry includes laboratory or other physical research and development in biotechnology, physical, and life sciences. It does not include economic, educational, engineering, operations, systems, or other nonphysical research. The Small Business Administration (SBA) defines an establishment (entity) as small in this industry if the business has fewer than 1,000 employees.[9]

Table 11. NAICS 54171 by Number of Employees

Size *(# of Employees)*	Num. of Entities	Receipts/Revenue *($1,000)*
Less than 5	5,385	2,392,627
5-9	2,135	2,886,410
10-19	1,622	4,661,128
20-49	1,435	8,903,136
50-99	857	9,811,043
100-249	841	17,549,575
250 or more	2,527	105,804,538
All Entities	**14,802**	**152,008,457**

[8] See TableID EC1700SIZEEMPFIRM, "ECN Core Statistics Economic Census: Establishment and Firm Size Statistics for the U.S.: Employment Size of Firms for the U.S.: 2017" at https://data.census.gov/cedsci/table?d=ECN%20Core%20Statistics%20Economic%20Census%3A%20Establishment%20and%20Firm%20Size%20Statistics%20for%20the%20U.S.&n=54171%3AN0500.00&tid=ECNSIZE2017.EC1700SIZEEMPFIRM

[9] See U.S. SBA's Size Standards Table, https://www.sba.gov/sites/default/files/files/Size_Standards_Table.pdf.

The 2017 Economic Census indicates that there are 14,802 entities classified in the NAICS 54171. Table 11 shows the breakdown of the research and development entities in the physical and life sciences industry by number of employees. Based on the data in Table 11, we estimate that all of these entities employ fewer than 1,000 employees and would qualify as small entities as defined by the SBA. Based on the annual receipts or revenue reported in the 2017 Economic Census, we estimate the average annual receipts or revenue per small entity in the industry is $10.4 million. We request comment or data to support other assumptions made in this analysis.

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

We estimate the cost per small entity to be $153, which is the cost of reading the rule establishing certain exemptions from the IND requirements. All affected entities are small as defined by the SBA. We do not anticipate this cost to be burdensome enough to create an incentive to leave the industry. In addition, about 99% of the cost savings of the proposed rule are attributed to sponsors of clinical investigations. Divided across 557 affected entities, we estimate that annualized cost savings per sponsor are about $6,300, more than 40 times the one-time cost of reading the rule.

C. Alternatives to Minimize the Burden on Small Entities

The proposed rule would provide the largest cost savings for all small entities. The alternative regulatory options would decrease or eliminate total cost savings to small entities. First, if there is no change in current regulations, small entities would not get any cost savings. Second, if FDA does not exercise enforcement discretion with respect to any studies evaluating a drug use of a food or cosmetic (in addition to not adopting the proposed rule), the burden on small entities would increase significantly compared to the baseline. Finally, if the proposed rule is modified to create an FDA-determined exemption but not a self-determined exemption, the cost savings to small entities would be positive, but about two percent less than estimated in our main analysis.