DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Food Labeling; Gluten-Free Labeling of Fermented or Hydrolyzed Foods

Docket No. FDA-2014-N-1021

Final Regulatory Impact Analysis

Final Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

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

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small firms may have annualized costs that do not exceed one percent of their annual revenue, we 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 issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $156 million, using the most current (2019) Implicit Price Deflator for the Gross Domestic Product. This rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

This rule requires that, for foods that are fermented or hydrolyzed or contain one or more fermented or hydrolyzed ingredients, and bear any of these claims: "gluten-free," "no gluten," "free of gluten," or "without gluten," the manufacturer must have records that demonstrate adequate assurance that the food, or fermented or hydrolyzed ingredient(s), is "gluten-free" in compliance with 21 CFR 101.91(a)(3). In addition, the rule requires documentation by the manufacturer that any potential for gluten cross-contact has been adequately assessed, and where such potential has been identified, that the manufacturer has implemented measures to prevent the introduction of gluten during the manufacturing process. The rule also provides that we will evaluate compliance of distilled foods, such as distilled vinegar, by verifying the absence of protein using scientifically valid analytical methods that can reliably detect the presence of protein or protein fragments in the food.

The costs of this rule are the costs to manufacturers of covered foods for testing ingredients for gluten, evaluating any potential for cross-contact, developing and carrying out written standard operating procedures (SOPs) for preventing gluten cross-contact if necessary, relabeling products that cannot be brought into compliance, and maintaining records of these activities for FDA inspection. We estimate total annualized costs of $7 million to $11 million for the 3% discount rate and annualized costs ranging from $7 million to $11 million at 7% discount rate. All costs are computed in 2018-dollar values.

The benefits of this rule are health gains for people with celiac disease using "gluten-free" labeled foods while maintaining a gluten-free diet. To examine the potential scope of these benefits, we simulate the harm done by dietary gluten intake from a gluten-free diet before and after the rule. Due to uncertainty in this simulation analysis, we describe benefits qualitatively. For the rule to break even with costs, the annualized benefits would need to be at least $8.8 million at a 3% discount rate and $9.1 million at a 7% discount rate. Based on our simulation analysis, the rule would break even with primary cost estimates discounted at 7% if at least 0.07% of estimated individuals with celiac disease following a gluten-free diet benefit from the rule each year.

Table 1. Summary of Benefits, Costs, and Distributional Effects of Final Rule (Millions)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2018	7%	10	
					2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative	The benefits of this rule are health gains for people with celiac disease using "gluten-free" labeled foods while maintaining a gluten-free diet. For the rule to break even with costs, the annualized benefits would need to be at least $8.8 million at a 3% discount rate and $9.1 million at a 7% discount rate. Based on our simulation analysis, the rule would break even with primary cost estimates discounted at 7% if at least 0.07% of estimated individuals with celiac disease following a gluten-free diet benefit from the rule each year.						
Costs	Annualized Monetized $millions/year	$9.09	$7.34	$11.46	2018	7%	10	
		$8.76	$7.14	$10.94	2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: Small Business: Wages: Growth:							

In line with Executive Order 13771, in Table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon based on 2016-dollar values. Based on these costs, this final rule would be considered a regulatory action under EO 13771.

Table 2. EO 13771 Summary Table (in $ Millions 2016 Dollars, Over an Infinite Time Horizon)

Item	Primary Estimate (7%)	Lower Estimate (7%)	Upper Estimate (7%)
Present Value of Costs	$107.12	$89.37	$130.02
Present Value of Cost Savings	0	0	0
Present Value of Net Costs	$107.12	$89.37	$130.02
Annualized Costs	$7.50	$6.26	$9.10
Annualized Cost Savings	0	0	0
Annualized Net Costs	$7.50	$6.26	$9.10

C. Comments on the Preliminary RIA and Our Responses

The Agency did not receive any comments on the preliminary regulatory impact analysis.

D. Summary of Changes

While we received no public comments on the preliminary economic analysis, we have made the following change to our final analysis: We previously computed monetized health benefits based on a simulation analysis. Due to underlying uncertainty in this analysis, we now describe these benefits as simulated and exclude them from our total accounting. Instead, we highlight the impact of the final rule by discussing how these simulated benefits could break even with estimated costs.

Compared to the preliminary analysis, the final regulatory impact analysis updates inputs into our simulated benefits analysis and costs model with more recent data. The analysis now uses wage, population, and QALY data from 2018. The final analysis also incorporates updated peer-reviewed estimates of celiac disease prevalence and accounts for potential changes to baseline consumption of covered products following publication of the 2013 gluten-free final rule.

II. Final Regulatory Impact Analysis

When presenting our estimates of input values, we use average values for readability. All results presented are for average values of inputs, rounded to the nearest 100th significant figures in the text. The "Uncertainty and Sensitivity Analysis" section presents the probability distributions of inputs and the Monte Carlo simulation that we use to form our final estimates.

A. Background

Gluten is a protein found in wheat, barley, rye, and their crossbred hybrids [1]. Wheat gluten is generally recognized as safe [2], and gluten-containing grains are staples in the food supply [3]. Because of this, many foods contain gluten-containing grains or ingredients derived from them. Additionally, many foods contain gluten, even though they do not contain any gluten-containing ingredients, because of cross-contact with these ingredients [3]

People with celiac disease may be harmed by consuming gluten. The way for them to avoid harm is to maintain a gluten-free diet [1]. Many foods bear a "gluten-free" labeling claim to advertise that their food is safe for individuals with celiac disease.

B. Market Failure Requiring Federal Regulatory Action

Before FDA published a final rule defining the term "gluten-free" and establishing requirements for the voluntary use of the term in labeling[1], approximately 5% of foods labeled "gluten-free" contained more than 20 ppm of gluten [4]. Due to testing limitations specific to fermented and hydrolyzed foods, additional requirements for these foods are needed to help ensure that individuals with celiac disease are not misled and receive truthful and accurate information when these foods are labeled "gluten-free." Although it is not possible to verify this with testing, we estimate that one percent of fermented and hydrolyzed foods contain more than 20 ppm of gluten. As we show below in the detailed analysis in section II.F.b., Estimating Baseline Gluten Consumption, this means that about 4,326 individuals diagnosed with celiac disease consume such foods daily and are at risk of harm due to a 50 mg daily gluten intake from such food represented to be "gluten-free." We use the term "harm" in

[1] This rule, now codified at 21 CFR 101.91, published in the Federal Register on August 5, 2013 at 78 FR 47154.

this analysis to reflect the morphological damage that 50 mg of gluten per day has been shown to cause in those with celiac disease [5, 6]. This rule would reduce or eliminate that morphological damage by limiting the "gluten-free" label to foods that are manufactured in a way that minimizes their gluten content.

C. Purpose of the Rule

In the Federal Register of August 5, 2013 (78 FR 47154), we published a final rule that defines the term "gluten-free" and establishes requirements for the voluntary use of the term in food labeling. The rule is codified at 21 CFR 101.91 (the gluten-free food labeling final rule). This rule is a response to limitations of analytical method technology for enforcement of 21 CFR 101.91 when "gluten-free" claims are made about certain foods.

Our regulation at 21 CFR 101.91 helps protect individuals with celiac disease by setting several requirements, one of which is that foods that bear a "gluten-free" labeling claim must have less than 20 parts per million (ppm) of gluten due to the unavoidable presence of gluten or from an ingredient derived from gluten-containing grain that has been processed to remove gluten. This regulation states that FDA will enforce the 20 ppm requirement using a valid test method that can reliably detect the presence of 20 ppm gluten in a variety of food matrices. At this time, there is uncertainty in interpreting the results of current gluten test methods for fermented and hydrolyzed foods on a quantitative basis that equates the test results in terms of intact gluten. Thus, FDA does not have the ability to test such foods to determine their compliance with 21 CFR 101.91.

D. Baseline Conditions

The baseline for this economic analysis is full compliance with 21 CFR 101.91 for all foods that are not fermented or hydrolyzed, and the current market situation for foods that are fermented or hydrolyzed. We estimate how the rule might change health status and manufacturer costs from this baseline.

E. Costs of the Rule

In order to demonstrate that the food is gluten-free before fermentation or hydrolysis, we expect that most manufacturers would test their incoming ingredients or obtain Certificates of Analysis from their ingredient suppliers. While testing is not required nor even expected in all circumstances, it is a

reliable way to demonstrate that an ingredient is gluten-free, so we include estimates for the costs of testing. To the extent that some manufacturers rely on other appropriate verification regarding their ingredients, this analysis may overestimate the total cost. Once a manufacturer evaluates its manufacturing process, if it determines that there is the potential for gluten cross-contact, it must document its implementation of measures to prevent gluten cross-contact and maintain these records so they can be made available to FDA. For the purpose of this analysis, we are calling the entire process of evaluating the potential for gluten cross-contact, and development and implementation of measures to prevent cross-contact "developing written standard operating procedures (SOPs) for preventing gluten cross-contact." Some manufacturers may decide not to maintain the "gluten-free" label on their products and, instead, relabel the product to remove this claim.

Therefore, for the purpose of this analysis, the costs of this rule are represented as those costs necessary to test the ingredients for gluten, evaluate the potential for gluten cross-contact and, if necessary, develop written SOPs for preventing gluten cross-contact, relabel products that cannot be brought into compliance, and maintain records of these activities for FDA inspection.

Our estimates of the numbers of manufacturers are based on the number of food products that would be covered by the rule. In November 2017 we searched the FoodEssentials database recently rebuilt and renamed Label Insight [7] for foods that are hydrolyzed, fermented, or contain fermented or hydrolyzed ingredients, and bear the claim "gluten-free," "no gluten," "free of gluten," or "without gluten" and found about 2,500 products that would be affected by the rule. Based on our understanding of the market and experience with the percentage of the food market covered by this database, we estimate that it has at least half of all products that would be covered by the rule, so that there would likely be, at most, 5,000 products affected by the rule.

We do not have data that would allow us to determine how many products are produced in each facility, so we assume that each product and its production line would be tested separately and would require a separate evaluation and SOP. If multiple products are produced in the same facility and can share testing, evaluation, SOPs, and paperwork, then costs would be less than these estimates.

We do not know how many of these products are already being manufactured using gluten-free ingredients and/or with a process designed to prevent gluten introduction through cross-contact. A 2011 survey of food industry practices [8] shows that about 45% of all food production facilities have a

written allergen control plan, and about 39% require certificates of analysis for ingredients. Given that manufacturers of foods labeled "gluten-free" are marketing to customers who care more about gluten cross-contact, we estimate that about 75% of the 5,000 foods with a "gluten-free" labeling claim already have a written plan for preventing the introduction of gluten into the food product that includes the testing of ingredients and also procedures for evaluating and preventing gluten cross-contact. Therefore, we estimate that testing and SOP development costs would be incurred for about 1,250 products. Even facilities that already have an allergen control plan would need to make records available to FDA for inspection and copying, so we estimate that these costs would be incurred for about 5,000 products.

a. Testing Costs

As described above, to demonstrate that food is gluten-free before fermentation or hydrolysis, we expect that most manufacturers would test their incoming ingredients or obtain Certificates of Analysis from their ingredient suppliers. Gluten testing can be done by sending ingredient samples to a testing company and by using test kits on site. Test kits must first undergo method validation for the testing situation in which they are to be used [9]. We assume that a manufacturer that begins a program of testing the gluten content of an ingredient would start by sending several samples to a lab and obtaining method validation for a test kit for the ingredient. This is a one-time cost.

After paying the startup cost, the manufacturer would then use test kits to test the ingredient on a regular basis and may also send one or two samples a year to an outside lab for testing. This is a recurring annual cost. We estimate that an average of two ingredients per universal product code (UPC) would be tested in this manner. Most foods affected by this rule are those that contain a single hydrolyzed or fermented ingredient, and an ingredient supplier would complete testing before fermentation or hydrolysis of the ingredient. Other products contain several ingredients that would be tested before fermentation or hydrolysis.

It is also possible that manufacturers would obtain a Certificate of Analysis from their ingredient supplier showing that the ingredient does not contain gluten instead of testing the ingredients themselves. To the extent that a single supplier can provide tested ingredients to multiple manufacturers, the cost of the rule would be lower than our estimates.

Testing companies charge between $68 and $110 per sample, with a best estimate of about $75 [10, 11]. The average of these estimates is about $84 ([68+75+110]/3=84.33), and we also estimate that

manufacturers would spend about $28 per sample to collect the ingredient and mail it to the lab,[2] for a total cost per lab test of $112 (84.33+27.81=112.14).

Manufacturers would test between 2 and 12 samples of each ingredient [9], for an average of 7 samples and an average testing cost of $ (112.14*7=784.99). Method validation costs between $1,000 and $10,000, with a most likely cost of $2,500 [12], for an average cost of $4,500 ([1+2.5+10]/3=4.5).

This results in an average total one-time cost of $5,285 per ingredient tested (785+4,500=5,285). We use Excel's PMT function to annualize this cost over ten years with a cost of capital of 7% and find that the annualized cost is $752 per year per ingredient. If the cost of capital was 3%, the annualized cost would be approximately $620 per ingredient.

Test kits cost about $11 each and take 10 minutes to use [10]. The average wage rate in the food manufacturing industry is $37.34 after adding benefits and overhead [11] which means that the total cost of using a test kit is about $17.22 (11+[37.34*10/60]=17.22). We estimate that manufacturers would use test kits between twice a year and once a week, with a best estimate of once a month, per ingredient. We therefore use a triangular distribution with minimum 2, maximum 50, and peak 12. This yields an average of about 21 ([2+12+50]/3=21.3) test kits used per year, at an annual cost of $367.43 per ingredient (17.22*21.33=367.43). In addition to using test kits, companies would send between zero and two samples of each ingredient annually to an outside lab, for an average annual cost of $112 (112*[0+2]/2 = 112). Adding up these two costs yields total recurring costs of $480 per ingredient on average (367+112=480).

Adding the average recurring costs to the average annualized one-time costs yields total annual testing costs of $1,232 per ingredient at a 7% cost of capital and $1,099 at a 3% cost of capital that can be attributed to this rule.

With the average estimate of 1,250 UPCs requiring testing, and an average of two ingredient tests per UPC, we estimate the total economic costs of testing that result from this rule to be about $3.0 million at a 7% cost of capital and $1.5 million at a 3% cost of capital.

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[2] A USPS Medium Flat Rate Box costs $12.35 and will hold most food samples. The cost of the food ingredient sent for testing will be about $10. Ten minutes of labor at $32.75 an hour will be required to mail the sample. 12.35+10+(32.75x10/60) =27.81

Table 2 summarizes the variables and the results of the calculations explained above, using mean values for all variables:

Table 2. Testing Cost Summary

	Per Ingredient	Total
Startup		
Initial tests	7	
Testing Cost	$785	
Method Extension	$4,500	
Total One-time	$5,285	$13,200,000
Annualized		
3% Cost of Capital	$620	$1,500,000
7% Cost of Capital	$752	$1,900,000
Recurring		
Number of kits used	21	
Cost of Kits	$367	
Number of Lab Tests	1	
Cost of Lab Tests	$112	
Total Recurring	$480	$1,200,000
Total Annual Cost of Testing: 3%	$1,099	$2,700,000
Total Annual Cost of Testing: 7%	$1,232	$3,000,000

b. Cost of Development and Implementation of Measures to Prevent Cross-Contact

We have estimates for the time and expense of developing allergen control procedures for facilities producing one product. We use these estimates as the cost of evaluating gluten cross-contact risk and developing gluten control procedures for a single UPC. To the extent that multiple UPCs can be made in the same controlled facility, these estimates overstate the expected cost of the rule.

Based on our expert elicitation, we estimate that it would take six to eight hours to develop and implement facility-specific procedures for gluten control. This would require the time of professional staff, at a cost of $119 per hour (this amount includes benefits and overhead costs) [11]. We also estimate that companies would spend between $0 and $2,000 on allergen control equipment, for a per-UPC average estimate of $1,834 (7*119+1,000=1,834) [13]. This is a one-time cost. We use Excel's PMT function to annualize this cost over ten years with a cost of capital of 7% and find that the

annualized cost is $261 per year per UPC. If the cost of capital was 3%, the annualized cost would be approximately $215 per UPC.

Facilities without pre-existing procedures would require regular training in the proper use of the procedures. We estimate that it would take approximately two hours per year to train an employee in the correct use of the procedures. This would require two hours of manager time and two hours per employee, with five to 15 employees being trained. We also estimate that it would take an additional 0.7 hours of manager time per year to update the procedures. This yields an average annual training cost of $1,068 per UPC ((2.7*119.12) +(2*10*37.34) =1,068).

Adding the average recurring costs to the average annualized one-time costs yields total annual SOP costs of about $1,329 per UPC at a 7% cost of capital (261+1,068=1,329) and $1,283 per UPC at a 3% cost of capital (215+1,068=1,283) that can be attributed to this rule.

With the average estimate of 1250 UPCs requiring the development and implementation of measures to prevent the introduction of gluten into fermented or hydrolyzed food, we estimate the total economic costs of SOP development and implementation that result from this rule to be about $1.7 million at a 7% cost of capital (1,329*1,250=1,661,902) and $1.6 million at a 3% cost of capital (1,283*1,250=1,604,257).

Table 3. SOP Cost Summary

	Per UPC	Total
Startup		
Hours for Development	7	
Equipment Cost	$1,000	
Total One-time	$1,834	$2,300,000
Annualized		
3% Cost of Capital	$215	$269,000
7% Cost of Capital	$261	$326,000
Recurring		
Manager Hours for Updating	0.7	
Manager Hours for Training	2	
Worker Hours for Training	20	
Total Recurring	$1,068	$1,300,000
Total Annual Cost of Testing: 3%	$1,283	$1,600,000
Total Annual Cost of Testing: 7%	$1,329	$1,700,000

c. Relabeling Costs

Some manufacturers may decide that it is not possible or economical to make their product in a way that complies with this rule. They may also discover that the products are still not gluten-free after they start a program aimed at compliance with this rule. In either case, they would then remove the "gluten-free" label from the product.

Testing of foods with "gluten-free" claims has shown that 5% of such foods contain more than 20 ppm of gluten [4, 14, 15]. Therefore, we estimate, as an upper bound, that 5% of foods covered by this rule would be relabeled.

According to the FoodEssentials database [7] in 2018, there were 2,514 of 271,872 UPCs had a "gluten-free" claim affected by this rule, so we estimate that 0.9% of all foods have such a "gluten-free" claim (2,514/271,872=0.9%). Because 5% of foods covered by this rule might have to be relabeled, we estimate that 0.05% of all foods would need to be relabeled (0.9%*5%=0.046%).

We believe that removing the claim in response to this final rule will impose minimal, if any, reformulation costs because the least costly way to comply with the rule will be relabeling. However, it is possible that producers may make the business decision to start using an allergen control plan to eliminate gluten cross-contact, instead of relabeling. This would involve incurring costs to change the production process, train workers, and possibly test ingredients and change suppliers. However, we estimate that producers would engage in these activities only when profits from doing so are higher than the profits from relabeling and abandoning the market for "gluten-free" labeled foods. We believe the same reasoning applies to reformulation, which producers may decide to undertake by substituting ingredients used before hydrolyzation/fermentation.

We cannot predict what proportion of manufacturers might decide to pursue allergen control or reformulation, which depends on a product's market as well as how the product introduces gluten into its production process. However, because we estimate relabeling would apply to 0.05% of foods affected by this rule and because we expect the majority of manufacturers to relabel, the proportion of foods pursuing either allergen control or reformulation would be <0.025% (less than 50% of 0.05%). This proportion is relatively small and, given that we do not know the division between allergen control and reformulation, we refrain from making additional estimates which may be highly uncertain.

We used FDA's Labeling Cost Model [16] to calculate the potential new labeling costs implied by the rule. The model calculates the cost of a new label based on the product type, label type, compliance time, and inflation. The compliance costs of labeling laws are lower if the required changes can be coordinated with planned label changes. Manufacturers will have one year to comply with the rule. The Labeling Cost Model uses a three- to four-year timeline for normally scheduled redesign, which means that only some of the labeling changes required by this rule can be coordinated with planned labeling changes.

The costs per UPC of relabeling depend on the exact printing method, the amount of packaging in inventory, the labor costs of managing the relabeling process and other variable factors. Because these costs cannot be known with certainty, the Labeling Cost Model reports a low and high cost estimate for any required label change. The lowest estimated cost for relabeling during a 12-month compliance period is $150 per label UPC for branded products. The highest estimated cost for a 12-month compliance period is $13,230 per label UPC for private label products. And, the midpoint of average estimated cost, adjusting for inflation, is about $7,000 per UPC.

We entered the value of 0.05% of all foods requiring relabeling into the Labeling Cost Model, and the result was that it calculated relabeling costs for 347 UPCs.

With a 12-month compliance period, the Labeling Cost Model estimates that 89% of branded product labels and 95% of private label product labels of labels using the claim would have to change their labels earlier than planned. If 347 labels are affected, the rule would affect 317 unscheduled label changes and 30 scheduled label changes. The midpoint of estimated label cost per UPC for a 12-month compliance period is $7,101 for unscheduled changes and $289 for scheduled changes. The higher cost reflects both discarded inventory and overtime or rushed order charges.

With 89% to 95% of the 347 UPCs incurring the full cost, and the remainder incurring lesser costs, the cost of relabeling due to the rule, adjusted for inflation to 2019, is estimated to be approximately $2.4 million (347*$7,101*92% ≈ $2.4 million). This is a one-time cost. We use Excel's PMT function to annualize this cost over ten years with a cost of capital of 7% to estimate that the rule would, if finalized, cost approximately $340,000 per year due to label changes. If the cost of capital was 3%, the annualized cost would be approximately $280,000.

d. Paperwork Costs

The rule would require manufacturers to maintain records showing that their food products meet the requirements of the rule. The manufacturers would need to make these records available to FDA for inspection and copying.

We estimate that the manufacturers would satisfy the recordkeeping requirements of this rule by maintaining records of their tests or other appropriate verification procedures, their evaluation of the potential for gluten cross contact, and their standard operation procedures for preventing gluten cross-contact. It is also possible that manufacturers would comply with this rule by obtaining Certificates of Analysis or test results from their suppliers instead of conducting the testing themselves. In that case, the suppliers rather than the manufacturers would incur the paperwork burdens related to collecting samples for the tests, and the manufacturers would still incur the paperwork burdens related to maintaining records of the tests, in the form of the Certificates of Analysis or test results themselves. If one supplier provides ingredients for multiple manufacturers, then the paperwork burden would be less than these estimates.

The estimates presented here are averages. We anticipate that the records kept would vary based on the type of ingredients used. Some manufacturers, such as those producing fermented dairy products, would likely maintain fewer records, because one bulk ingredient can be used for many UPCs. Other manufacturers, such as those producing foods with fermented or hydrolyzed grains, legumes, or seeds, would likely maintain more extensive records, because those products contain more ingredients and a greater variety of ingredients.

The costs of testing are detailed earlier in section II.E.a. of this analysis. We estimate that, in addition to these costs, the rule would require 30 minutes of work per test to process and file the test results so that they can be made available to FDA. The average wage rate in the food manufacturing industry is about $37.34 after adding benefits and overhead [11], so this work would cost $37 per hour, for an additional paperwork cost of $18.50 per test.

The one-time method extension requires an estimated average of seven tests per ingredient, so with two ingredients per product, the associated paperwork cost would be $259 per UPC (7*0.5*37*2=259). This is a one-time cost. We use Excel’s PMT function to annualize this cost over ten

years with a cost of capital of 7% and find that the annualized cost is $37 per year per UPC. If the cost of capital was 3%, the annualized cost would be approximately $31 per UPC.

We estimate that the manufacturers would use 21 test kits annually on average, per ingredient so the associated paperwork cost would be $777 per UPC (21*0.5*37*2=777). We estimate that the manufacturers would conduct one outside test annually on average per ingredient, so the associated paperwork cost is $37 per UPC (1*0.5*37*2=37).

The costs of developing and updating SOPs are detailed earlier in section II.E.b. of this analysis. We estimate that, in addition to these costs, the rule would require one hour of work per UPC to maintain the updated SOP records, for a cost of $37 per year.

The total annualized paperwork costs per UPC from testing and SOP development are $896 at a 7% cost of capital and $889 at a 3% cost of capital.

While we estimate that 3,750 manufacturers already have testing programs and written procedures in place for gluten control (5,000-1,250=3,750), it is not clear that these manufacturers are maintaining these test results and written procedures a way that would align with the requirements. Therefore, we estimate that all 5,000 UPCs would incur these paperwork costs, for a total cost of $4.5 million per year with a cost of capital of 7% and $4.4 million per year with a cost of capital of 3%.

Table 4. Paperwork Cost Summary

	Per UPC	Total
Startup		
Method Extension Records	$259	$1,300,000
Annualized		
3% Cost of Capital	$31	$150,000
7% Cost of Capital	$37	$186,000
Recurring		
SOP Update Records	$37	$187,000
Test Kit Records	$777	$4,000,000
Lab test Records	$35	$187,000
Total Recurring	$807	$4,300,000
Total Annual Cost of Paperwork: 3%	$889	$4,450,000
Total Annual Cost of Paperwork: 7%	$896	$4,480,000

e. Total Costs

The total annualized cost of the testing, evaluation, SOPs, relabeling, and paperwork is $9.0 million at a 7% cost of capital and $8.7 million at a 3% cost of capital.

F. Benefits of the Rule

To examine the potential scope of the benefits of the rule, we simulate the harm done by dietary gluten intake from a gluten-free diet before and after the rule. We simulate the number of people harmed under the baseline (full compliance with the existing 21 CFR 101.91 for other products) and the amount by which they are harmed. We then compare the results of these simulated benefits to the costs of the rule using a break-even approach.

a. Number of Individuals with Celiac Disease on a Gluten-Free Diet

According to a study based on the 2009 to 2014 National Health and Nutrition Examination Survey of non-institutionalized civilian population in the U.S. [17, 18], 0.21% of the population have been told by a medical professional that they have celiac disease.[3] In December of 2018, the Census estimated the civilian non-institutionalized population aged over 6 years to be about 298.6 million, so we multiply the population by the percentage of individuals with celiac disease to estimate that there are about 627,000 people diagnosed with celiac disease in the U.S. (298,600,000*0.21%=627,000).

We do not know the harm that is caused by foods that contain 20 ppm or more gluten and bear the "gluten-free" claim in individuals with celiac disease who are only partially compliant with the gluten-free diet. Therefore, we must exclude them from the analysis. There have been many estimates of the percentage of individuals with celiac disease who fully comply with the gluten-free diet. The estimates of compliance range from 45% to 80%. Recent studies where nutritionists interviewed care-takers or children aged 2-19 years and adult patients aged above 18 years of age concluded that about 79 to 82% of celiac patients had good or excellent adherence with a gluten-free diet, meaning that they knowingly eat gluten once a month or less. The two separate studies focused on patient categories that were either children (2-19 years) or adults patients who were aged above 18 years [19, 20]. For the study

[3] This weighted prevalence estimate is the difference between the percent of population with diagnosed and undiagnosed celiac disease (0.72%) and the percent of population with undiagnosed celiac disease (0.51%). In the Analysis of Uncertainty, we show how we generated a probability distribution to reflect uncertainty in this estimate.

focusing on children below 19 years old, 66 children were followed for two years beginning August 1, 2014 to July 31, 2016. These children were included if they had a confirmed diagnosis of celiac disease and a standardized evaluation of adherence by a registered dietitian (M.D.R.) with expertise in pediatric celiac disease. The second study had a sample of 29 adults diagnosed with celiac disease before they were 4 years old and their adherence to celiac disease diet was compared with patients diagnosed with celiac disease as adults.

Owing to the small size of these studies we use a triangular distribution with minimum 45%, maximum 82%, and a peak of 79%. This yields an estimated average of ~69% compliance ([45+82+79]/3=68.7). Multiplying this percentage by the number of individuals diagnosed with celiac disease, we find that there are approximately 432,600 individuals diagnosed with celiac disease complying with a gluten-free diet (627,000*69%=432,600).

This does not include people who choose to remain on a gluten-free diet for reasons other than medically diagnosed celiac disease. There are many individuals with celiac disease without a medical diagnosis of celiac disease. Many of these people may have self-diagnosed and chosen to eat a gluten-free diet, which means that they would also benefit from the rule. We do not have enough data to include them in the core analysis, but we discuss how the benefits of the rule increase if they are included in section II.F.e, Other Potential Benefits.

b. Estimating Baseline Gluten Consumption

To estimate the baseline gluten intake, we used gluten testing results of food currently labeled "gluten-free," data on diets from the NHANES survey [21], and data on the percentage of "gluten-free" foods that have fermented or hydrolyzed ingredients to simulate gluten-free diets and the daily gluten intake from those diets. These simulated diets consisted of a random selection from fermented or hydrolyzed "gluten-free" foods, non-fermented or hydrolyzed "gluten-free" foods, and inherently gluten-free foods not labeled as "gluten-free" and therefore not covered by these rules, such as raw agricultural commodities, in random amounts matching the observed distribution of serving sizes.

Comments from the Celiac Sprue Association to the gluten-free rulemaking [4] included test results for 1,000 food products labeled "gluten-free." The amount of gluten detected, if any, was reported for each individual food. Of these, 49 had levels of gluten above 20 ppm. A more recently published article cited a study that retrospectively examined information from product packaging for

328 foods tested for gluten content by Gluten Free Watchdog, LLC that only looked at products labeled gluten-free. Of the products reviewed, 297 did not include an allergen advisory statement for wheat or gluten on product packaging and only 31 products included such a statement. Of the 297 without allergen advisory statement, 39 contained quantifiable gluten at or above 5 ppm with 12 products testing at 20 ppm or above[22]. This is the best source of data we have of foods labeled "gluten-free"; we lack the information that would allow us to ensure a representative sample of all "gluten-free" foods and of fermented and hydrolyzed foods. Other studies [14, 15] have reported a slightly larger percentage of foods whose gluten content exceeds 20 ppm, but they were not as comprehensive and did not report data for individual food products.

Because we currently know of no scientifically valid analytical method effective in detecting and quantifying with precision the gluten protein content in fermented and hydrolyzed foods in terms of equivalent amounts of intact gluten proteins, we assume that the distribution of gluten content in these foods is similar to the distribution of gluten content in tested foods. It is possible that the lack of testing has resulted in a situation where fermented and hydrolyzed foods have a greater chance of containing 20 ppm or more gluten than foods that can be tested. In this case, the benefits of this rule would be greater than the benefits we calculate. Based on data from 2014, the NHANES Total Nutrient Intakes tables show that the average consumer consumed 15 servings of food and drink daily. The NHANES Individual Foods data show the grams of each food or beverage that was consumed. Serving sizes of beverages are larger than serving sizes of foods, and there were many outliers of very large serving sizes from beverages. While we recognize the issue of gluten in beer, most beverages are rarely a source of gluten. Using the serving sizes of both foods and beverages to estimate the distribution of serving sizes of "gluten-free" food would have caused the serving sizes to be biased upwards, which would cause us to overestimate gluten intake. Therefore, we removed water, beverages, juices, milk, and raw watermelon from the data, which resulted in a mean serving size of about 82 grams. We then fit a gamma distribution to these values.[4]

We then simulated 100,000 gluten-free diets using the @RISK program [23]. Each diet consisted of a mix of inherently gluten-free unlabeled foods and foods labeled "gluten-free". Foods labeled

[4] The gamma distribution was chosen because the data were extremely right-skewed, with many small values but no negative values, and the gamma distribution is flexible enough to fit such data without truncation. We found that the distribution of food serving sizes had a shape parameter of approximately 0.86 and a scale parameter of approximately 95.

"gluten-free" consisted of foods that met the requirements of 21 CFR 101.91 and the tested "gluten-free" foods.

We do not know what proportion of the average gluten-free diet comes from inherently gluten-free unlabeled foods and foods labeled "gluten-free", but we do know that some consumers rely on their own research of safe foods and others purchase products with "gluten-free" labels almost exclusively. We therefore drew the proportion of labeled food in each diet from a uniform distribution with a minimum of 0 and a maximum of 1. Each diet consisted of 15 random draws of an inherently gluten-free unlabeled food or a food labeled "gluten-free", according to that diet's proportion of labeled foods. The amount of each food eaten was drawn from the previously defined gamma distribution.

To determine the fraction of foods labeled "gluten-free" that are fermented or hydrolyzed or have fermented or hydrolyzed ingredients, we searched the FoodEssentials database [7], a comprehensive survey of food products sold in nationwide in the U.S., for foods with claims about gluten that would be affected by the rule: "gluten-free," "no gluten," "free of gluten," and "without gluten." The search also included variations of these claims within larger sentences, such as "No milk, soy, or gluten." We refer to all such claims as "gluten-free" claims. We found 11,108 such foods in November 2017.

We then searched the foods with "gluten-free" claims for ingredients that are fermented or hydrolyzed. For the purposes of this search, we considered autolyzed yeast extract to be a hydrolyzed food, based on the text of 21 CFR 102.22. We searched for foods with one or more of the following words in the ingredients list: hydrolyzed, autolyzed, yeast extract, fermented, beer, brandy, cheese, cider, fish sauce, kimchi, kombucha, miso, pepperoni, pickle, salami, sauerkraut, vinegar, vodka, whisky, wine, and yogurt. We found 2,514 such foods, which means that approximately 23% of all foods with a "gluten-free" claim contain one or more ingredients that are fermented or hydrolyzed (2,514/11,108=0.226). We lack information that would allow us to further refine this percentage; therefore, we assume that 23% of all labeled "gluten-free" foods consumed are fermented or hydrolyzed or contain fermented or hydrolyzed ingredients.

We modeled all products covered by 21 CFR 101.91 as containing up to 19.9 ppm gluten (uniform distribution between 0 and 19.9). We assumed zero gluten from inherently gluten-free food and from sources other than food. Changing this assumption to add trace amounts of gluten from these foods

or other sources would have increased the percentage of diets that contained more than 50 mg gluten. This would have inflated the estimate of the number of people harmed at the baseline.

The highest amount of gluten that can be safely consumed each day by individuals with celiac disease is not known and is likely to vary from person to person. For the purposes of the economic analysis, we choose a value for harm of 50 mg of gluten per day because this amount has been shown to cause morphological damage to most individuals with celiac disease in a double-blind, placebo-controlled challenge study [5]. This choice produces a tendency toward underestimation of the true scope for benefits of the rule, because it underestimates the baseline harm. As we explain in section II.F.b., Other Potential Benefits, individuals with celiac disease are probably harmed by consuming smaller amounts of gluten daily, and this rule would also reduce intake at those levels.

The simulation results in roughly 1.6% (1,600) of the simulated diets containing more than 50 mg of gluten. This result is not significantly affected by our choice of the gamma distribution to model the amount of each food consumed. A simulation where people consumed exactly 82 grams of all foods resulted in about 1.8% (1,800) of diets containing more than 50 mg of gluten. We choose the gamma-distribution simulation because it is a more accurate model and lessens the chance of overestimating the benefits of the rule. However, since the publication of the gluten-free final rule (published in the Federal Register on August 5, 2013 at 78 FR 47154, now codified at 21 CFR 101.91), consumption patterns of fermented and hydrolyzed foods may have changed. In particular, consumers may have reduced their consumption of these products since they may not have had confidence in the labeling of hydrolyzed and fermented products bearing the "gluten-free" claim due to the issues with evaluating compliance. Because we do not have information that would allow us to estimate changes in consumption of fermented and hydrolyzed foods over time, we model this parameter as a triangular distribution with minimum 0.5%, peak 1%, and maximum 1.6%.[5] We use a wide range with 1.6% as a maximum to account for potential decreases in consumption of covered products that may have followed the first gluten-free final rule.

[5] Due to the dearth of reliable data, we use probability distributions at multiple points in the analysis. Given that less than 2% of the simulated diets reach the 50 mg threshold, the tails of distributions have outsized importance. Fairly small deviations from uniformity could produce quite different estimates of how many diets exceed the threshold, so it is unclear whether the 1.6% estimate is meaningful.

We multiply the estimate of the percentage of gluten-free diets with 50 mg or more of gluten daily by the number of individuals with celiac disease on a gluten-free diet to produce an estimate of approximately 4,326 individuals with celiac disease harmed by the consumption of fermented or hydrolyzed foods carrying the "gluten free" label and containing 20 ppm or more gluten as part of their diet (1%*432,600=4,326). For purposes of this analysis, this assumes that each of these diets contains daily consumption of at least some fermented or hydrolyzed products labeled as "gluten-free."[24][6]

c. QALY Loss from Baseline Consumption and Social Cost

Our approach to estimating the benefits of being in good health (health benefits) involves the use of Quality-Adjusted Life Years (QALYs). QALYs can be used to measure the loss of well-being that an individual suffers due to a disease or condition. The QALY calculation does not include the cost of medical expenditures caused by the illness in question. QALYs range from 0 to 1, where 0 is equivalent to death and 1 is equivalent to perfect health for one year.

A number of methods have been constructed to measure QALYs. The studies that we reference use the EQ-5D health index to calculate changes in QALY as a result of celiac disease. The EQ-5D index allows us to estimate an individual's disutility from being ill in terms of the number of QALYs lost due to that illness. As shown in Table 5, the EQ-5D scale consists of five domains, with 3 levels for each domain, that assess an individual's mobility, ability to perform self-care activities, ability to perform usual activities (such as going to work or school), level of pain and discomfort, and level of anxiety and depression as a result of their medical condition.

Table 5. EQ-5D Health Status Classification System

Domain	Attribute Level	Description
Mobility	1	I have no problems walking about
	2	I have some problems walking about
	3	I am confined to bed

[6] Implicit in this approach is the assumption that no consumers with celiac disease who comply with strict diets would be confused by claims (e.g., 'processed to remove gluten') that are permitted for products that do not meet the requirements of this rule and thus might contain more than 20 ppm of gluten. Providing support for this assumption is consumer research that shows that people with celiac disease insist on words or symbols that say 'gluten-free' and distrust other claims.

Self-Care	1	I have no problems with self-care
	2	I have some problems washing or dressing myself
	3	I am unable to wash or dress myself
Usual Activities	1	I have no problems with performing my usual activities
	2	I have some problems with performing my usual activities
	3	I am unable to perform my usual activities
Pain/Discomfort	1	I have no pain or discomfort
	2	I have moderate pain or discomfort
	3	I have extreme pain or discomfort
Anxiety/Depression	1	I am not anxious or depressed
	2	I am moderately anxious or depressed
	3	I am extremely anxious or depressed

We found three articles that reported EQ-5D scores for individuals with celiac disease [25-28]. These studies either compared the reported health outcomes of celiac who did not follow a gluten-free diet to those who adhered to a gluten-free diet, or they compared the change in health outcomes for patients newly diagnosed celiac who switched to a gluten-free diet after their diagnosis. The reported increases in EQ-5D scores as a result of adhering or switching to a gluten-free diet were 0.20, 0.21, and 0.27. Given that treatment for celiac disease is the removal of gluten from the diet, we conclude that exposing an individual with celiac disease to the levels of gluten in the average diet results in a mean QALY loss of 0.23 ([0.2+0.21+0.27]/3=0.227).

We do not have dose-response relationships for gluten in people with celiac disease, so we do not know how the QALY loss that such individuals experience from consuming 50 mg of gluten daily compares with the QALY loss from consuming a non-gluten-free diet. Given the morphological changes caused by 50 mg of gluten [7], we assume a low estimate that 50 mg of gluten causes 5% of the harm a non-gluten-free diet would cause.

We have an estimate that inadvertent partial compliance with the gluten-free diet causes a QALY loss of 0.09 [26]. We use this to generate a high estimate that 50 mg of gluten causes 30% of the harm a non-gluten-free diet would cause.

We have studies showing that prolonged exposure to amounts of gluten smaller than 50 mg daily causes some individuals with celiac disease to report symptoms that lower their quality of life [29, 30],

but these studies do not provide EQ-5D scores. We use these studies to generate a best estimate that 50 mg of gluten causes 10% of the harm a non-gluten-free diet would cause.

The mean of the triangular distribution generated by these estimates is 15% ([5+30+10]/3=15). This means that, on average, an individual with celiac disease who consumes more than 50 mg of gluten daily as a result of exposure to gluten from foods carrying the "gluten free" label that contain 20 ppm or more gluten suffers a QALY loss of 0.035 (0.23*15%=0.0345).

Multiplying the estimate of the number of individuals with celiac disease harmed by the estimate of the QALY loss of the harm produces an estimate of approximately 160 QALYs lost each year from "gluten-free" food with levels of gluten of 20 ppm or higher (4,326*0.035=151.4).

We monetize this QALY value using the guidelines for regulatory impact analyses from the U.S. Department of Health and Human Services [31]. The central 2018 value of a QALY, at a 7% discount rate, is $871,000 and $524,000 at 3% discount rate. Using this value, the current social loss from food labeled "gluten-free" with 20 ppm or more gluten is approximately $131.5 million annually (151*$871,000=$131,521,000) at 7% discount rate, and $79 million annually (151*$524,000=$79,124,000) at 3% discount rate. Dividing the annual estimate of social loss by potential total number of persons with celiac disease (i.e. 4,326), the estimated cost per person ranges between $18,000 and $30,000 per person per year. Since these costs are relatively high, it may be unlikely that morbidity of such magnitude would fail to prompt consumers to shift to less-painful food options even in the absence of the rule. For this reason, we are hesitant to describe the results of our simulated analysis as quantitative. We instead use a break-even discussion to qualitatively compare these simulated benefits to costs of the rule.

Table 6 summarizes the variables and the results of the calculations explained above, using mean values for all variables:

Table 6. Baseline Harm Calculation Summary

Variable	Mean Value
Non-institutionalized Civilian Population Over 5 Years Old	298,600,000
Percent of Population Diagnosed with Celiac Disease (CD)	0.21%
Individuals Diagnosed with CD	627,000
Percent of CD-Diagnosed Individuals on "gluten-free" Diet	69%

CD-Diagnosed Individuals on "gluten-free" Diet	432,600
Percent of "gluten-free" Diets Above 50 mg *	1.0%
CD-Diagnosed Individuals on "gluten-free" Diet Consuming >50 mg of gluten *	4,326
QALY Loss for Untreated Celiac Disease *	0.23
Severity of 50 mg Compared to Untreated *	15%
QALY Loss for >50 mg of gluten *	0.035
Annual QALY Loss from High-gluten Food *	151
Value of QALY loss (3% Discount rate) *	$524,000
Value of QALY loss (7% Discount rate) *	$871,000
Total Annual Baseline Harm (3% Discount rate) *	$79,000,000
Total Annual Baseline Harm (7% Discount rate) *	$131,500,000
* Simulated analysis; results not claimed as regulatory baseline.	

d. Gluten Consumption with Rule

Next, we simulated gluten-free diets after the rule. We assumed full compliance with the rule. Even under the unlikely worst-case scenario where all "gluten-free" labeled products contain up to 19.9 ppm gluten and people consume those products exclusively rather than inherently gluten-free unlabeled food, not one of 100,000 simulated diets contained more than 50 mg of gluten daily. The average diet had 12 mg of gluten daily. Therefore, for the purpose of this simulated analysis, we assume that all harm associated with the consumption of more than 50 mg of gluten daily by individuals with celiac disease, who comply with a gluten-free diet, would be ended by the rule even under the worst-case scenario.

If the rule results in some foods that previously bore a "gluten-free" claim no longer being able to bear the "gluten-free" claim, consumers who are seeking "gluten-free" packaged foods may change their consumption away from those products. To the extent that consumers preferred those products to the gluten-free products they may now choose instead, our analysis should consider the possibility of consumers' lost pleasure from such substitution. We lack the information to quantify this effect, because among other reasons, consumers' behavior may be driven by habit, and their preferences may not be consistent over time. As a result, consumers may make different choices regarding products they like that may have negative consequences for their health over time. Due to this uncertainty about consumer behavior, the health benefits simulated above do not account for potential lost utility, thus increasing overall uncertainty in our total simulated benefits.

e. Other Potential Benefits

NHANES survey data from 2009 to 2014 show that 1.11% of the U.S. civilian non-institutionalized population is on a gluten-free diet without a diagnosis of celiac disease [17]. As previously noted, 0.21% of individuals have been told by a medical professional that they have celiac disease. However, after including undiagnosed individuals who test positive for celiac disease with a serological test, the estimated prevalence of celiac disease in the U.S. population of both diagnosed and undiagnosed individuals is 0.72% [17]. This estimate suggests there are many undiagnosed individuals with celiac disease in the population. As a result, we believe that many of these people would gain the same benefit from a gluten-free diet as individuals diagnosed with celiac disease.

Individuals with undiagnosed celiac disease on a gluten-free diet would suffer the same harm from foods carrying the "gluten free" label that contain 20 ppm or more gluten as individuals with diagnosed celiac disease, but we do not know how many people on a gluten-free diet actually have celiac disease and how closely they comply with the diet. It is possible that a significant percentage of people on a gluten-free diet are individuals with undiagnosed celiac disease who have good compliance with the diet. If this were the case, then the harm done by foods carrying the "gluten free" label that have 20 ppm or more gluten would be much greater than we estimate in the preceding simulation analysis.

As discussed above, 0.14% of the U.S. population consists of people with diagnosed celiac disease who comply with a gluten-free diet (0.21%*68%=0.14%). For example, chosen for ease of presentation, if one-sixth of the people on a gluten-free diet were individuals with undiagnosed celiac disease with good compliance, then there would be an additional 0.1% of the population benefiting from the rule (0.68/6=0.103).

In addition to eliminating diets with more than 50 mg of gluten per day, the rule would reduce the percentage of diets with levels of gluten that might cause lesser harm. About 1.7% of simulated baseline gluten-free diets have between 20 mg and 50 mg of gluten per day. After the rule is in place, about 0.9% of diets have between 20 mg and 50 mg of gluten per day. If levels of gluten between 20 mg and 50 mg per day cause health problems for individuals with celiac disease, then those health problems would be reduced as a result of the rule.

The distribution of gluten in the simulated diets is extremely right-skewed. Over two-thirds of all diets with more than 50 mg of gluten per day had over 100 mg of gluten per day. In our simulation analysis, we assumed that all diets with more than 50 mg of gluten per day cause the same harm.

However, diets with larger amounts of gluten, such as 100 mg per day, may cause substantially more harm.

Untreated celiac disease can cause premature mortality in addition to losses in quality of life [1]. We do not have any information on the mortality effects of smaller doses of gluten, but it is possible that prolonged exposure to 50 mg of gluten or more also causes premature mortality. By removing this source of gluten, the rule may benefit individuals with celiac disease by preventing early death in addition to the benefit from improved quality of life.

In addition to the harm done to quality of life, untreated celiac disease can cause increased medical expenses. However, we do not know the additional medical expenses incurred by people who are complying with a gluten-free diet but who are exposed to gluten from hydrolyzed or fermented foods currently labeled "gluten-free." We believe that these medical costs are small compared to the QALY loss, but reducing these medical costs is an additional benefit of this rule.

There are many people who choose a gluten-free diet for reasons other than celiac disease. For example, people who do not suffer from celiac disease but who are allergic to wheat often use the "gluten-free" label to quickly identify foods that are free from the wheat proteins that trigger their allergic reactions. These people would also benefit from the rule. Anyone who is on a gluten-free diet for any reason would benefit from the reduction in search costs, if they start using and trusting the "gluten-free" label as a result of this rule.

f. Break-even Analysis

Our simulated benefits analysis showed that the primary annualized benefits of this rule could potentially range from $71.9 million at a 3% discount rate to $119.2 million at a 7% discount rate. For the rule to break even with costs, the annualized benefits would need to be at least $8.8 million at a 3% discount rate and $9.1 million at a 7% discount rate. Put differently, the simulated benefits would have to be overestimated thirteen-fold before they would fail to offset the costs of the rule at a 7% discount rate. Of the estimated population of 432,600 individuals with celiac disease complying with a gluten-free diet, the rule would break even with primary costs discounted at 7% if at least 0.07% of these individuals benefited each year ($9.1 million/$30,000 = 303 individuals; 303/432,600 = 0.07%). While these results should be interpreted with caution given the uncertainty underpinning our simulated

benefits, they suggest that the health benefits would need to be minimal for the final rule to fail to break even with costs.

G. Distributional Effects

We do not anticipate any significant distributional effects as a result of this regulation. The costs are split between consumers and business owners or shareholders, while the benefits go to the subset of consumers who are currently suffering from health problems.

H. International Effects

We do not anticipate any significant effects of this regulation on international trade. Domestic and foreign manufacturers pay equal compliance costs for each product they sell in the US.

I. Uncertainty and Sensitivity Analysis

In Tables 3, 4, 5, and 6 of this document and elsewhere, we present point estimates. While this is a convenient way to summarize the effects or potential scope of the rule and explain our calculation, the use of point estimates neglects the large degree of uncertainty intrinsic to the underlying analysis. In Table 7 of this document, we present the results of a Monte Carlo simulation of uncertainty for the final estimates of annual costs of the rule and for the simulated analysis regarding the scope of potential benefits.

All parameters are defined as probability distributions. In our Monte Carlo simulation, we use samples from the probability distributions rather than using the mean values. The randomly chosen numbers are used to form a final estimate. This procedure is repeated 10,000 times, and the results are ranked from lowest to highest. We report the distribution for each input parameter, and the 5^{th} percentile, mean, and 95^{th} percentile of the simulated results.

We relied on NHANES survey estimates of 22,277 people for a prevalence estimate of 0.21% of the population diagnosed with celiac disease. The standard error of this sample will be approximately 0.03% ((0.21%*99.862%/22,277) ^ 0.5=0.029%). Therefore, we use a normal distribution with a mean of 0.21% and a standard deviation of 0.03%. We truncate this distribution at zero, because there cannot be a negative percentage of individuals with celiac disease.

As we described above, the estimate for compliance with a gluten-free diet is a triangular distribution with minimum 45%, peak 79%, and maximum 80%.

Our 100,000 simulations of the diets before the rule were split into ten simulation runs of 10,000 diets each. The percentage of diets with more than 50 mg of gluten before the rule varied from 1.4 to 1.8 across simulation runs, with most results clustered around 1.6. We describe this parameter as a triangular distribution with minimum 0.5%, peak 1%, and maximum 1.6%. We use a wide range with 1.6% as a maximum to account for potential decreases in consumption of covered products that may have followed since the final rule on gluten-free labeling of food published in 2013 (codified at 21 CFR 101.91).

As described above, three estimates of QALY loss from untreated celiac disease are 0.20, 0.21, and 0.27. We draw the QALY loss from a triangular distribution with minimum 0.20, peak 0.21, and maximum 0.27. We draw the percentage harm that 50 mg of gluten causes compared to a non-gluten-free diet from a triangular distribution with minimum 5%, peak 10%, and maximum 30%.

We drew the cost of lab tests from a triangular distribution with minimum $96, peak $103, and maximum $138, reflecting the sum of testing and handling costs. We drew the number of products requiring new testing from a discrete uniform distribution with minimum 0 and maximum 2500.

We drew the number lab tests ordered in the first year from a discrete uniform distribution with minimum 2 and maximum 12. We drew the cost of method extension from a triangular distribution with minimum $1,000, peak $2,500, and maximum $10,000.

We drew the annual number of test kits used per UPC from a triangular distribution with minimum 2, peak 12, and maximum 50. We drew the annual number of lab tests ordered from a discrete uniform distribution with minimum 0 and maximum 2.

We drew the number of products requiring new SOPs from a discrete uniform distribution with minimum zero and maximum 2500. We drew the cost of allergen control equipment from a uniform distribution with minimum $0 and maximum $2,000.

The labeling cost model produced low, midpoint, and high estimates. Annualized at a 7% cost of capital, these are $0.19 million, $0.34 million, and $0.56 million, respectively. We drew labeling costs from a triangular distribution with low, peak, and high values equal to these low, mid, and high estimates.

Table 7 shows these results. The "Low" column shows the low estimates for the inputs and the 5th percentile of the simulation results. The "Median" column shows the medians for the inputs and simulation results. The "High" column shows the high estimates for the inputs and the 95th percentile of the simulation results. All results are rounded to the nearest million for clarity and to prevent a false impression of precision.

Table 7. Analysis of Uncertainty Summary

Variable	**Low**	**Median**	**High**
Cost of Lab Test	$96	$103	$138
Products Requiring New Testing	0	1,250	2,500
Products Requiring New SOP	0	1,250	2,500
Allergen Control Equipment Costs	$0	$1,000	$2,000
Initial Lab Tests	2	7	12
Method Extension Cost	$1,000	$2,500	$10,000
Number of Test Kits Used Annually	2	21	50
Number of Annual Lab Tests	0	1	2
Annualized Relabeling Costs (Millions)	$0.19	$0.34	$0.56
Annual Costs: 3% discount (Millions)	**$7**	**$9**	**$11**
Annual Costs: 7% discount (Millions)	**$7**	**$9**	**$11**
Percent of Population Diagnosed with CD	0.16%	0.21%	0.26%
Percent of CD Diagnosed People on "gluten-free" Diet	45%	69%	80%
Percent of "gluten-free" Diets Above 50 mg *	0.5%	1%	1.6%
QALY Loss for Untreated Celiac Disease *	0.2	0.227	0.27
Average Severity of 50 mg Compared to Untreated *	5%	15%	30%
Value of QALY: 3% discount rate *	$244,000	$524,000	$ 797,600
Value of QALY: 7% discount rate *	$407,000	$871,000	$1,326,000
Annual Benefits: 3% discount (Millions) *	**$31**	**$72**	**$152**
Annual Benefits: 7% discount (Millions) *	**$53**	**$119**	**$254**
* Simulated analysis; results not claimed as benefits of the rule.			

Because many uncertainties could not be measured, Table 7 should not be seen as a complete characterization of the uncertainty underlying the analysis.

A big driver of uncertainty is likely to be the fact that there is a wide range of sensitivity to gluten among individuals with celiac disease. If each individual has a unique "dose-response" to gluten exposure, then there would also be individual variability with respect to QALY loss. There is no

research that defines the distribution of gluten sensitivity across the population [32], so our simulated benefits analysis reflects averages from small and limited studies.

J. Analysis of Regulatory Alternatives

We have identified two regulatory alternatives:

1. Prohibit the "gluten-free" claim on all fermented and hydrolyzed foods; and

2. Limit the requirements of the rule to a subset of fermented and hydrolyzed foods.

1. Prohibit the "Gluten-Free" Claim on Fermented and Hydrolyzed Foods

Another regulatory alternative is to prohibit the "gluten-free" claim on all fermented and hydrolyzed foods, due to the uncertainty in interpreting the results of current gluten test methods for fermented and hydrolyzed foods on a quantitative basis that equates the test results in terms of intact gluten in order to verify their compliance with the 20 ppm requirement.

This alternative would mean that manufacturers who are making good-faith attempts to produce gluten-free fermented or hydrolyzed foods, or foods that contain such ingredients, would not be able to distinguish these products from ordinary products by using the "gluten-free" claim. While manufacturers could develop statements that might be informative about gluten content, these statements may not be helpful for consumers without a clear a regulatory standard. Without certainty about gluten content, celiac consumers might avoid such products to decrease their risk of gluten exposure. Moreover, without a regulatory standard, firms may not be able to differentiate themselves adequately by offering "gluten-free" products. This alternative would reduce the incentives for manufacturers to market such products. They would not have the option of demonstrating compliance by documenting appropriate ingredients and processes and may be forced to bear relabeling costs if they currently make a "gluten-free" claim. If we assume that all affected products would incur no other costs but those to relabel, the annualized cost of the rule at a 7% discount rate is $0.3 million.

This alternative could reduce the chances that individuals with celiac disease are exposed to potentially harmful gluten fragments from fermented and hydrolyzed foods if individuals avoid these foods entirely. However, the removal of such products from the "gluten-free" market would reduce the dietary options and/or increase the search costs of people with celiac disease. Alternatively, celiac

consumers may continue consuming such products at risk to their health due to lack of labeling clarity. This could reduce their compliance with a gluten-free diet and result in health problems.

2. Limit the Requirements of the Rule to a Subset of Fermented and Hydrolyzed Foods

Another regulatory alternative is to make the requirements of this rule apply only to a subset of fermented and hydrolyzed foods containing ingredients deemed to be at high risk of gluten cross-contact, for example legumes, grains, and seeds. This alternative would have lower costs than the rule, but also lower benefits.

According to the FoodEssentials database [7], approximately one-fifth of all fermented or hydrolyzed foods labeled "gluten-free" contain legumes, grains, and seeds,[7] and, according to FDA subject matter experts, these foods are at a higher risk of gluten cross-contact than vegetables, meats, and dairy due to the way they are typically transported and stored. We estimate that the total annualized costs of this alternative (if the rule only applied to foods that are or contain hydrolyzed legumes, grains, or seeds) would be about $7.2 million less than the total costs of the rule ($9 million * 0.8 = $7.2 million).

III. 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 small firms may have annualized costs (over ten years at a seven percent discount rate) that do not exceed one percent of their annual revenue, we certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. This section serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

[7] This figure excludes distilled vinegar.

A. Description and Number of Affected Small Entities

The Small Business Administration (SBA) publishes size standards for industry categories of firms defined by North American Industry Classification System (NAICS) codes. SBA defines each NAICS code's small business threshhold either in terms of sales revenue or number of employees of a firm. Using the 2019 SBA size standards[8] in conjunction with the Statistics of U.S. Businesses (SUSB) counts of firms in each NAICS code by revenue and employment size,[9] we estimate the numbers of covered small firms by industries that may be affected by the final rule. Our first step is to broadly identify the number of affected industries by different sizes using annual total receipts and number of employees. Table 8 lists these industries by both annual receipts and number of employees based on broad three- and four-digit NAICS code categories.

Next we estimate proportion of small industries that will be affected by the rule. We determine that between 97 to to 98 percent of industries coverd by this rule are composed of small businesses by SBA standards (number of employees). We do not have information that would allow us to estimatethe proportion of firms in each industry involved in the production of fermented and hydrolyzed foods. Table 8 shows estimated counts of small firms that may be affected by the rule.

Table 8: Summary of Potential Industry Sectors Affected by the Rule

2012 NAICS Code	NAICS Industry Description	Number of Employees	Number of Firms	Total Annual Revenue ($ millions)	Revenue per Firm ($ millions)	Size Standard (Number of Employees)
311	Food Manufacturing	<10	12,500	10,658	0.85	500
311	Food Manufacturing	10-19	3,439	10,526	3.1	500
311	Food Manufacturing	20-99	3,849	54,954	14.3	500
311	Food Manufacturing	100-499	1,291	116,558	90.3	500
311	Food Manufacturing	500+	542	646,864	1,193	500
3121	Beverage Manufacturing	<10	2,943	2,015	0.68	750

[8] Small Business Association. Table of Size Standards. Aug 19, 2019. Available from: https://www.sba.gov/document/support--table-size-standards

[9] We use the 2012 SUSB, the last release that contained revenue data, and inflate revenues to 2019-dollar values using the GDP deflator. Available from: https://census.gov/data/datasets/2012/econ/susb/2012-susb.html

3121	Beverage Manufacturing	10-19	606	1,817	3.0	750
3121	Beverage Manufacturing	20-99	592	5,988	10.1	750
3121	Beverage Manufacturing	100-499	133	10,479	78.8	750
3121	Beverage Manufacturing	500+	79	94,651	1,198	750

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

We calculate costs to small firms based on our primary estimates. Table 9 breaks down the annual cost of implementing the rule per UPC per firm. A key assumption we make in this analysis for small businesses is that each firm may incur compliance costs for one UPC product only. We assume that all covered small entities would incur one-time costs to validate the gluten free tests. Some covered small entities may also incur a one-time capital investment cost and a one-time SOP training cost, as well as recurring annual testing and labeling costs. In our assessment of one-time costs, most of these would be less than $500 per UPC per firm, and these costs may not be incurred for all small businesses.

Table 9: Annual Cost of Complying to Gluten Free Rule per Firm per Product

Compliance Activities	**Primary Estimate**
Gluten Testing and Validation	$2,464
Standards of Operating Procedures (SOP)	$1,330
Relabeling	$978
Paperwork	$896
Annualized total cost per UPC product	$5,667

We use 2019-inflated annual firm receipts from the 2012 SUSB. The firm receipts are used to estimate the magnitude of costs as a percent of the revenues of potentially affected small firms. We consider costs per firm exceeding one percent of annual revenues to be a substantial impact. Table 10 shows our estimate of the annual costs as a percentage of revenue for small firms, broken down by broad industry categories expected to be affected by the rule. We expect costs as a percentage of annual revenue to range from about 0% to 0.8% for each of the industries that would potentially be affected by the rule. These percentages are likely overestimates for firms with <10 employees, because our cost estimates assume that at least ten employees will require training.

Table 10: Annual costs of rule compliance per firm as a percentage of small firm annual revenue

2012 NAICS Code	NAICS Industry Description	Number of Employees	Costs as a percent of annual revenue (primary)
311	Food Manufacturing	<10	0.7%
311	Food Manufacturing	10-19	0.2%
311	Food Manufacturing	20-99	0.0%
311	Food Manufacturing	100-499	0.0%
311	Food Manufacturing	500+	0.0%
3121	Beverage Manufacturing	<10	0.8%
3121	Beverage Manufacturing	10-19	0.2%
3121	Beverage Manufacturing	20-99	0.1%
3121	Beverage Manufacturing	100-499	0.0%
3121	Beverage Manufacturing	500+	0.0%

C. Alternatives to Minimize the Burden on Small Entities

Based on annual firm receipts and number of employees per firm, most firms in potentially affected industries would qualify as small entities. Our analysis shows that small firms would not be impacted significantly. Nevertheless, since the rule requires the firms to voluntarily declare whether or not their products are gluten-free, it also allows flexibility on how firms can integrate proposed changes into their business plans. For example, firms could coordinate labeling changes with already-scheduled relabelling activities, which may reduce annual costs per UPC by nearly 40 percent.

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