DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Nonprescription Drug Product with an Additional Condition for Nonprescription Use

Docket No. FDA- [2021-N-0862]

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Executive Summary

The final rule establishes requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). Compared to traditional nonprescription drug products, which consumers must be able to self-select and use based on their labeling, this approved ACNU, in addition to the labeling, will ensure the appropriate self-selection, the appropriate use, or both of a nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. We expect this rule will increase options for applicants to develop and market safe and effective nonprescription drug products and will increase consumer access to appropriate, safe and effective drug products.

We estimate a reduction in access costs to consumers who could transfer from a prescription to a nonprescription drug product with an ACNU. Our primary estimate for this item is $33.62 per consumer per purchase with a range of $0 to $67.23. We also quantify the value of the potential reduction in the number of meetings with applicants that will occur during the approval process. This estimate includes benefits to us and industry. Our primary estimate is $68,773.11 per applicant with a range of $56,332.65 to $81,763.56. We do not aggregate our estimates of benefits because of the high uncertainty about the number of applicants, applications, potential approvals, and purchases that might occur; and consumer preferences to switch drug products. However, we present estimates in the uncertainty section of this analysis.

Although an applicant will incur the costs to develop and submit an application for a nonprescription drug product with an ACNU, for this analysis, we assume that applicants submit applications only when they believe that the profits from the approval will exceed the costs of the application. We lack information to monetize these potential profits and costs.

Monetized costs include a one-time cost of reading and understanding the rule per interested party in pursuing this path for their drug products. We do not aggregate these estimates for more than one interested party because of the high uncertainty about the number of interested parties over this time horizon. The primary estimate equals $1,156.74 with a range of $533.88 to $1,779.60.

Government-sponsored and commercial insurance payers may experience cost savings because the availability of nonprescription drug products with an ACNU may decrease insurance claims and, potentially, future medical costs. For example, access to drug products under this new pathway will allow consumers to treat some medical conditions using nonprescription drug products with an ACNU without the supervision of a practitioner licensed by law to administer such drugs. We do not estimate such cost savings due to lack of data.

I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104-121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). OIRA has determined that this final rule is not a significant regulatory action under Executive Order 12866 Section 3(f)(1).

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. This rule would establish the requirements for a nonprescription drug product with an additional condition of nonprescription use (ACNU). We cannot anticipate the number of applicants that would submit applications or the types of drug products that would be covered under such applications. However, we estimate the costs for any applicant to read and understand the rule would likely range between 0.04 percent and 0.12 percent of the gross receipts of very small applicants. Therefore, we certify that the final 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 estimates of anticipated impacts, 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 $183 million, using the most current (2023) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

The final rule establishes requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). Compared to traditional nonprescription drug products, which consumers must be able to self-select and use based on their labeling, this approved ACNU, in addition to the labeling, will ensure the appropriate self-selection, the appropriate use, or both of a nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug. We expect this rule will expand consumer access to certain drug products in a nonprescription setting and increase options for applicants to develop and market safe and effective nonprescription drug products.

Table 1 shows our quantified benefits. We estimate a reduction in access costs to consumers who could transfer from a prescription to a nonprescription drug product with an ACNU. Our primary estimate for this item is $33.62 per consumer per purchase with a range of $0 to $67.23. We also quantify the value of the potential reduction in the number of repetitive meetings with applicants that will occur during the approval process. This estimate includes benefits to FDA and industry. Our primary estimate is $68,773.11 per applicant with a range of $56,332.65 to $81,763.56. We do not aggregate our estimates of benefits because of the high uncertainty about the number of applicants, applications, potential approvals, and purchases that might occur; and consumer preferences to switch products. However, we present estimates in the uncertainty section of this analysis. In addition, although commercial and government-sponsored drug coverage plans will likely experience cost savings if their cost of coverage declines or if future medical costs decline, we do not estimate such cost savings due to lack of data.

Although an applicant will incur the costs to develop and apply for a nonprescription drug with an ACNU, for this analysis, we assume that applicants submit applications only when

they believe that the profits from the approval will exceed the costs of the application. We lack information to monetize these potential profits and costs.

Monetized costs include a one-time cost of reading and understanding the rule per interested party in pursuing this path for their drug products. We do not aggregate these estimates for more than one interested party because of the high uncertainty about the number of interested parties over this time horizon. The primary estimate equals $1,156.74 with a range of $533.88 to $1,779.60.

Government and commercial insurance payers may experience cost savings because the availability of nonprescription drug products with an ACNU may decrease the number of submitted insurance claims and, potentially, future medical costs. For example, access to drug products under this new pathway will allow consumers to treat medical conditions using nonprescription drug products with an ACNU without the supervision of a practitioner licensed by law to administer such drugs.

Table 1. Summary of Benefits, Costs and Distributional Effects of the Final Rule ($ millions 2023)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)							
	Annualized Quantified				2023			Quantified reduction in access costs per consumer purchase range from $0.0 to $67.23, and a primary estimate of $33.62
					2023			Quantified reduction in meetings between FDA and applicants

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
								ranges from $56,332.65 to $81,763.56 per applicant, and a primary estimate of $68,773.11
	Qualitative							
Costs	Annualized Monetized ($m/year)	$0.0	$0.0	$0.0	2023	7%	10 years	The reading and understanding one-time costs primary estimate is $1,156.74 and range from $533.88 to $1,779.60 per interested party.
		$0.0	$0.0	$0.0	2023	3%	10 years	
	Annualized Quantified							
	Qualitative	Interested firms will incur costs to develop and submit applications						
Transfers	Federal Annualized Monetized ($m/year)					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized ($m/year)					7%		
						3%		
	From/To	From:			To:			Potential cost savings to government and commercial insurers if coverage cost of medications decline.
Effects	State, Local or Tribal Government: No estimated effect. Small Business: The estimated costs to very small potential applicants in this industry range from 0.04 percent to 0.12 percent of gross receipts. Wages: No estimated effect. Growth: No estimated effect.							

C. Comments on the Preliminary Economic Analysis of Impacts and Our Responses

On June 22, 2022, we published the proposed rule "Nonprescription Drug Product with an Additional Condition for Nonprescription Use" (87 FR 31313). We received several

comments on the preliminary regulatory impact analysis of the proposed rule (PRIA) that accompanied the proposed rule. Below we group the comments by topic and offer a brief description of each along with our responses. The order of comments and responses is not a reflection of importance.

ACNU Studies:

(Comment) We received a few comments asserting that requiring applicants to conduct robust consumer studies to demonstrate a label alone is insufficient will add considerable time and cost. These comments further assert that these studies will preclude many companies from developing a nonprescription drug product with an ACNU.

(Response) Like all drug development programs, we acknowledge that development of a nonprescription drug product with an ACNU will require the applicant to expend resources. For an application for a nonprescription drug product with an ACNU, the rule requires an applicant to demonstrate the necessity and effect of the ACNU to ensure appropriate self-selection or appropriate actual use, or both. The applicant may need to conduct or reference adequate testing. For example, applicants may conduct consumer studies to demonstrate the necessity and effect of the ACNU. Consumer studies, however, may vary in cost, and such costs are uncertain. We have added uncertainty bounds of development costs to our analysis and without further information, we cannot adjust them to reflect any specific concerns.

We disagree that the costs to develop a nonprescription drug product with an ACNU will reduce treatment options. Without the rule, nonprescription drug products are limited to drugs that can be labeled with sufficient information to enable consumers to appropriately self-select and use the drug product without the supervision of a practitioner licensed by law to administer

such drug. Therefore, the rule has the potential to broaden the types of drug products that FDA could approve as nonprescription.

Payment:

(Comment) Some commenters believe the rule can decrease the economic disparity that exists due to prescription medications not being accessible without a practitioner licensed by law to administer such drugs and increase affordability and cost-effectiveness for the consumer. However, several other commenters, although generally supportive of the proposed rule, express concerns that the approval of nonprescription drug products with an ACNU may impact insurers' coverage of the prescription version of the drug product, and efforts should be taken to mitigate unintended consequences, including increased out of pocket costs for consumers that may impede consumer access. We received a comment suggesting that FDA should consult with Centers for Medicare and Medicaid Services (CMS) and other stakeholders to ensure Medicare beneficiaries can use nonprescription drug benefits to cover nonprescription drug products with an ACNU.

(Response) We understand that prices have a direct impact on consumers. However, an adverse effect on insurance coverage is not a certain outcome of the rule. While some health insurance plans may restrict drug coverage when one member of the drug class is made available for nonprescription use, some health insurance plans may continue to provide coverage for prescription version of the product despite availability of the nonprescription drug product with an ACNU. Drug coverage could differ depending upon which state the beneficiary lives in. For example, FDA is aware that some Medicare Advantage and Medicaid plans include supplemental benefits that provide a regular allowance for nonprescription drug products related to their conditions, whereas Medicaid beneficiaries can obtain coverage when the

nonprescription drug products are indicated by a health care provider. The FDA cannot stipulate what drugs insurers may cover or to what extent the drug may be covered.

Additionally, consumers' out-of-pocket costs are not always predictable. There is a misconception that prescription drug products are covered at low co-pays, but this may not always be the case. For example, an insurer may classify certain prescription drug products as non-preferred or non-formulary which are typically associated with higher out-of-pocket costs. Further, consumers without insurance or with high deductible insurance plans may benefit from the availability of nonprescription drug products with an ACNU because their out-of-pocket cost is usually higher for prescription drug products as compared to nonprescription drug products.

(Comment) We received one comment suggesting that FDA require price controls as a requirement to approve nonprescription drug products with an ACNU.

(Response) We disagree with setting price controls as a requirement to approve nonprescription drug products with an ACNU. FDA does not have the authority to approve or refuse to approve a drug product based on the prices set by manufacturers, distributors, or retailers.

(Comment) We received some comments wanting to see more details about the decrease in access costs.

(Response) We have included an appendix in the preliminary regulatory impact analysis and in this final analysis with details on how we model the potential decrease in costs.

(Comment) We received comments suggesting that if insurance does not cover the respective prescription drug product, generic competition in the prescription space will be effectively eliminated.

(Response) We disagree. The rule does not affect how health insurance plans cover prescription drug products. The rule includes a provision for simultaneous marketing of both the prescription and the nonprescription version with an ACNU. This provision may help with maintaining reimbursement status in the respective prescription markets.

Simultaneous Marketing:

(Comment) Several comments oppose simultaneous marketing citing financial concerns. Some comments oppose simultaneous marketing citing that it will inadvertently create a less competitive marketplace by failing to incentivize innovation in the prescription-to-nonprescription switch. Another comment argues simultaneous marketing of prescription and nonprescription drug products will severely reduce the opportunity for companies to recoup investment costs.

(Response) The proposed rule is intended to increase options for applicants to develop and market safe and effective nonprescription drug products. Without the rule, we may not be able to approve certain drug products that an applicant may seek to market on a nonprescription basis where labeling alone cannot communicate the information needed for the consumer to appropriately self-select, appropriately use, or both the drug product safely and effectively without the supervision of a practitioner licensed by law to administer such drug.

(Comment) Commenters suggested that the cost-savings to consumers we presented in the PRIA may be reduced if we allow simultaneous marketing. For example, simultaneous marketing will reduce the market size for the nonprescription product with an ACNU as consumers may purchase the prescription version instead.

(Response) We disagree and present evidence in the PRIA describing that roughly sixty percent of purchases for a nonprescription product are from completely new consumers. This evidence

from the average nonprescription markets suggests that the potential to attract new-to-therapy consumers is substantial.

Reporting:

(Comment) We received comments that the PRIA does not adequately account for the costs of quality assurance systems or implementing the reporting requirements.

(Response) We understand concerns about the potential costs of establishing and maintaining quality assurance systems. However, due to the uncertainty about the nature of ACNU failures that could occur, the likelihood, the number, and the cost, any estimate would be characterized by a substantial degree of uncertainty.

D. Summary of Changes

The main changes between the preliminary and final analysis relate to the updated estimates to account for inflation. The estimates in this final analysis reflect dollars in 2023, whereas estimates in the preliminary analysis reflected dollars in 2022. For example, the present analysis incorporates new released reports from the U.S. Census on the number and revenue of companies in the pharmaceutical preparation and manufacturing industry, and the Bureau of Labor Statistics on wages.

Other changes include a summary of comments related to the preliminary regulatory impact analysis and our responses. Lastly, we also clarified in the benefits section that the potential cost savings to government-sponsored plans and commercial insurance will likely be from avoided processing of drug-reimbursement claims, medical claims and the respective coverage, and potential future avoided medical claims as nonprescription drug products may

increase access and health outcomes. In sum, the potential cost-savings are broader than changes in reimbursement for a drug product.

II. Final Economic Analysis of Impacts

A. Background

We approve drug products to be marketed in the United States as either prescription or nonprescription drugs. Prescription status is reserved for drugs for which safe use requires supervision by a practitioner licensed by law to administer such drugs. By contrast, nonprescription drugs do not require supervision by such a practitioner to be used safely. Drug products with the same active ingredient may be made available simultaneously as both prescription and nonprescription if a meaningful difference (e.g., indication, strength, route of administration, dosage form, or patient population) exists between the two drug products.

Currently, nonprescription drug products are limited to drug products that can be labeled with sufficient information for consumers to appropriately self-select and safely use the drug product. A drug is misbranded if its labeling lacks adequate directions and warnings for use in accordance with section 502(f) of the FD&C Act.[1] This section authorizes FDA to issue regulations exempting a drug from the requirement for adequate directions for use when such directions are not necessary for the protection of public health. The final rule will amend FDA's regulations to exempt a nonprescription drug product with an ACNU from the requirements for adequate directions for use if certain conditions are met.

Currently, an applicant may propose that a drug product be approved as prescription or nonprescription. A request to change the marketing status of a drug from prescription to

[1] See section 502(f) of the FD&C Act (21 U.S.C. 352(f)).

nonprescription is commonly referred to as a prescription-to-nonprescription switch. To seek approval for a prescription-to-nonprescription switch, an applicant conducts requisite studies and submits a supplement to its NDA or a separate NDA to request to change the prescription drug product's status to nonprescription status. These studies may include a label comprehension study, a self-selection study, an actual use study, and human factors studies.

For nonprescription drugs currently on the market, the labeling provides information for the products for consumers to appropriately self-select or appropriately actually use the product, or both. However, for some drug products, labeling alone is not sufficient to ensure that a consumer can appropriately self-select or appropriately use, or both, a drug product in a nonprescription setting. For these drug products, an additional condition of nonprescription use (ACNU) will be needed to ensure appropriate self-selection or appropriate actual use, or both, by the consumer in a nonprescription setting.

This final rule will codify application requirements, labeling requirements, and postmarketing reporting requirements for nonprescription drug products with an ACNU. In addition, the rule will clarify that a prescription drug product and a nonprescription drug product with an ACNU could both be approved with the same active ingredient, indication, strength, route of administration, and dosage form and may be marketed simultaneously. The rule clarifies that the ACNU constitutes a meaningful difference between the two drug products. The rule does not preclude a direct-to-nonprescription pathway for nonprescription products with an ACNU (i.e., they will not necessarily need to be approved as prescription drugs first).

B. Market Failure or Other Distortion Potentially Addressed by Federal Regulatory Action

The main government failure this rule addresses is the lack of regulatory pathway for drug products to be approved with an ACNU. Thus, this rule will establish requirements,

including content and format requirements, for a nonprescription drug product with an ACNU. The regulation will also clarify that a prescription drug product with the same active ingredient, indication, strength, route of administration, and dosage form as a nonprescription drug product with an ACNU may remain on the market. In addition, a regulation is needed to add an exemption to the requirement for adequate directions for use for a nonprescription drug approved with an ACNU.

The final rule establishes requirements for nonprescription drug products with an ACNU for the protection of patients and to ensure the safety and efficacy of such marketed drugs. Establishing these requirements will also help us to operate more efficiently. For example, potential applicants have requested additional meetings with us per development program to discuss this topic; these types of individual meetings are time-consuming and use Agency resources. Multiple potential applicants have been asking the same types of questions, creating repetitiveness and inefficiencies. Because the rule addresses these and other questions, we anticipate that the rule will reduce or eliminate this burden for potential applicants and us.

C. Purpose of the Rule

The final rule will establish NDA and ANDA application requirements, labeling requirements, and postmarketing reporting requirements for a nonprescription drug product with an ACNU. Specifically, the rule will:

1. Establish requirements for applications for nonprescription drug products with an ACNU.
2. Clarify that a drug product with the same active ingredient, indication, strength, route of administration, and dosage form could be approved in separate applications as both a nonprescription drug product with an ACNU and a prescription drug product and be

simultaneously marketed. This is possible because the ACNU would serve as a meaningful difference between the prescription drug product and nonprescription drug product with the ACNU.

3. Clarify that generic applications (ANDAs) can have different ways to operationalize an ACNU.
4. Establish post-marketing reporting requirements requiring applicants to submit a report of ACNU failure to FDA.
5. Require labeling statements to alert consumers that the nonprescription drug product has an ACNU.

This rule will apply to NDAs and ANDAs for nonprescription drug products with an ACNU. An ACNU is one or more FDA-approved conditions that an applicant of a nonprescription drug product must implement to ensure consumers' appropriate self-selection or appropriate actual use, or both, of the nonprescription drug product without the supervision of a practitioner licensed by law to administer such drug when the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both. If labeling alone is sufficient for the drug product to be used safely and effectively by consumers, we would approve the drug as a nonprescription drug product, but not as a nonprescription drug product with an ACNU.

The rule has the potential to broaden the types of drug products that could be approved as nonprescription. Approvals under the rule will benefit consumers who do not have access to prescription drugs because of lack of insurance and may benefit some consumers with insurance by potentially reducing their access costs (for example transportation and time costs).

D. Baseline Conditions

Without the rule, certain candidate drug products approved as prescription-only will remain as prescription-only drug products or perhaps, not marketed at all. The rule will not affect drug products that have already switched to nonprescription status without an ACNU.

Industry has expressed interest to FDA about increasing consumer access to their approved prescription drug products by also marketing these products as nonprescription drug products. However, we lack complete information of potential applications for nonprescription drug products with an ACNU and the medical conditions they will treat.

E. Benefits

By establishing requirements for a nonprescription drug product with an ACNU, we anticipate benefits to industry from introducing a pathway to market a prescription drug product as a nonprescription drug product with an ACNU and benefits to consumers from expanded access to these drug products. We also anticipate cost-savings to consumers associated with reduced costs to access nonprescription drug products with an ACNU. There could also be cost savings to industry and us from a more efficient allocation of resources by reducing or eliminating the need for repetitive meetings and information requests.

. In addition, although we are not able to predict the number of applications that may be approved under the final rule, we present estimates of monetized benefits and cost savings in the sensitivity section. In the sensitivity analysis we make assumptions about the number of applications we might receive, the number of purchases that might occur, and consumer preferences to switch products. We also anticipate potential benefits and cost-savings to commercial insurers and government-sponsored insurance plans, but we lack data or adequate information to monetize them even in the sensitivity section.

1. Potential Reduction in Access Costs

We define access cost to be the monetized value for a consumer to obtain a medication. In our analysis, access costs include the time to see a doctor to obtain a prescription, including waiting time and other transportation costs. We also include co-pay and out-of-pocket costs in our estimate of access costs. We compare the baseline access costs to the access costs under potential scenarios with the final rule to estimate the potential benefits for each consumer purchase. In this analysis, we use the costs to obtain candidate prescription-only products as our baseline access cost. The rule will also allow for a direct approval of an application for a nonprescription product with ACNU without first requiring an application to market such drug product as prescription only. Although we expect the latter cases to be less common than a switch, in those cases, the benefits will include the full benefits from using the drug product relative to the baseline of not using the product at all. The sensitivity section in this analysis presents estimated benefits from these cases.

Table **2** summarizes the potential access costs for one consumer to obtain a nonprescription drug product with an ACNU that becomes available under the rule. We first estimate access costs for the baseline prescription scenario. We use 1 hour for transit and wait time from Temin (1992) as this is an appropriate time estimate because it was estimated using multiple drug products.[2] We assign a value to time using the hourly national average of $31.48 from the Bureau of Labor Statistics.[3] For the cost of transportation fare or fuel, we use estimates from Pfoh et al. (2008) which equal about $18.06 when updated for inflation. We use national

[2] Although studies on this subject are limited, we also considered another more recent study on switching antihistamine drug products from Nichol and Sullivan (2004) that indicates time used to obtain a prescription from a physician in the range of 2 to 3 hours. We do not use this study, however, because it may not be as representative as Temin (1992).

[3] https://www.bls.gov/oes/tables.htm

average co-pay per doctor visit from the Medical Expenditure Panel Survey (MEPS), which updated to 2023 dollars, averaged $29.84.[4] We assume that the change in the out-of-pocket per pack cost (e.g., bottle or box) is neutral and cancels out on average based on observations from past nonprescription switches.[5] Adding all of these access costs results in a baseline access cost of about $79.38 (= $31.48 in time costs + $18.06 in transportation expenses + $29.84 in copay for visit).[6]

Table 2.- Consumer Potential Reduction in Access Costs from Switching to a Nonprescription Drug Product with an ACNU ($ dollars 2023)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$79.38	$79.38	$79.38
Potential access costs	$45.76	$79.38	$12.15
Time cost per event	$19.68	$31.48	$7.87
Transportation cost per event	$11.17	$18.06	$4.28
Copay for visit	$14.92	$29.84	$0.00
Out-of-pocket per purchase	same	same	same
Access cost reduction per purchase relative to baseline	$33.62	$0.00	$67.23

Note: We round numbers to the nearest decimal in the table for presentation. We calculate the estimate of time costs in column three as 1 hour lost in transit and wait time multiplied by $31.48 hourly average wage. In column four, this estimate is 0.25 hours lost in transit and wait time multiplied by $31.48 hourly average wage. The primary estimate of time cost is the average of these two.

To estimate the maximum reduction in access costs for a product that would require minimal consumer effort to be eligible to purchase a nonprescription product with an ACNU, we

[4] Available at: https://meps.ahrq.gov/data_stats/summ_tables/insr/national/series_1/2016/tif5.pdf and https://meps.ahrq.gov/data_stats/summ_tables/insr/national/series_3/2016/tiiif5.pdf.

[5] We use data from the Medical Expenditure Panel Survey to estimate the change in out-of-pocket expenditures for a sample of drugs that switched from prescription to nonprescription status. We do so by comparing average expenditures before and after a marketing status switch. The data show that for the four markets examined (Lamisil, Pepcid, Mucinex, Plan B), there was an increase in out-of-pocket expenditures of $16 per package (bottle, box, etc.) on average. By contrast, we also observe that for four other markets (Prilosec, Miralax, Xenical, Prevacid) there was a decrease of about $12 per package (bottle, box, etc.). However, when aggregating all drugs and all years, the overall change is nearly zero. For this reason, we assume there is no change in out-of-pocket expenditures. See the Technical Appendix for additional information.

[6] Adding the out-of-pocket for the drug product would increase the total cost by about $30. Although the latter number may seem high, most of these products are initially branded, then nonprescription by the branded firm, and generic after that. For a deeper discussion on out-of-pocket trends, see Berndt and Newhouse (2012) p. 242.

estimate access costs of $12.15 (= $7.87 in time costs + $4.28 in transportation expenses + $0 in copay for visit). Compared to the baseline, the maximum cost reduction would equal $67.23 (= $79.38 – $12.15).

For the lower bound, we assume there is no change in transport and waiting time relative to the baseline. This lower bound may reflect cases where interaction with a pharmacist occurs and may take the same amount of time as with a physician. However, we note that ACNUs could incorporate different technologies and do not necessarily have to involve interactions with pharmacists. For our primary estimate of the reduction in access costs we average the upper and lower reduction in access costs, which results in $33.62.

In the sensitivity analysis, we make simplifying assumptions about the number of purchases to present estimates of potential benefits of the rule.

2. Meetings with Industry and FDA

We received several questions from industry about the process to market a prescription drug product as a nonprescription drug product with an ACNU. Based on this experience, we anticipate that the final rule will save resources equivalent to about 3 to 4 meetings per application. The reduction in this allocation of resources could result in cost-savings to both industry and us. In Table 3 we summarize our estimates.

Our records for the review of nonprescription drug products (with no ACNU) indicate that it takes an average of 55 FDA staff hours per meeting including time before, during, and after the meeting. For our upper-bound estimate, we use the fully loaded (wages that account for overhead) hourly wage from our office of budget records of $173.63 for CDER and calculate that our cost savings from eliminating these meetings equal $38,198.60 (= 4 meetings x 55 hours per meeting x $173.63 fully loaded hourly wage) per potential applicant. Similarly, we estimate the lower-bound

cost savings to us equals $28,648.95 (= 3 meetings x 55 hours per meeting x $173.63 hourly wage). The primary estimate is $33,423.78 (= 3.5 meetings x 55 hours per meeting x $173.63 hourly wage).

Table 3. Cost Savings from Fewer Meetings per Application ($ dollars 2023)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Number of meetings that could be avoided per application	3.5	3	4
FDA hours per meeting	55	55	55
Fully loaded wage FDA	$173.63	$173.63	$173.63
Cost to FDA	$33,423.78	$28,648.95	$38,198.60
Applicant hours per meeting	55	55	55
Fully loaded wage applicants	$177.78	$167.78	$187.78
Labor costs to applicants	$34,222.65	$27,683.70	$41,311.60
Transportation, lodging, and other expenses	$1,126.68	$0.00	$2,253.36
Cost to applicants	$35,349.33	$27,683.70	$43,564.96
Total reduction in meeting costs (FDA + applicants)	$68,773.11	$56,332.65	$81,763.56

Note: Estimates per application. Numbers are rounded to nearest decimal.

We assume that applicants also spend 55 hours in total on each meeting with us, including time before, during, and after the meeting. We use a fully loaded mean hourly wage of $187.78 (= $93.89 x 2 to account for overhead) from the Bureau of Labor Statistics occupational employment records for general operations managers in the pharmaceutical industry (North American Industry Classification System (NAICS) 325400, occupation code11-1021).

We estimate an upper-bound of meeting-time cost savings per application of about $41,311.60 (= 4 meetings x 55 hours per meeting x $187.78 mean wage per hour). In addition, we calculate cost savings from avoided lodging and transportation of $2,253.36 for all four meetings (= 4 meetings x $563.34 lodging and transportation per meeting). The combined upper-bound cost savings per application equals $43,564.96.

For our lower-bound estimate of meeting-time cost savings, we use the fully loaded median hourly wage of $167.78 (= $83.89 x 2) for general operation managers (occupation code 11-1021). Thus, our lower-bound estimate of cost savings to applicants equals about $27,683.70 (= 3 meetings x 55 hours x $167.78 wage). In this case, we do not add lodging and transportation because we assume that applicants will submit letters or call us instead of meeting in person.

Our primary estimate of meeting-time cost savings equals $34,222.65 (= 3.5 meetings x 55 hours per meeting x $177.78 average wage per hour between upper and lower wage). In addition, we calculate cost savings from avoided lodging and transportation of $1,126.68, the average between lower and upper bounds for this item. The combined primary cost savings estimate per application to the applicant equals $35,349.33.

Adding these benefits for potential applicants and us, on average, we estimate cost-savings from fewer meetings costs per application equal $68,773.11 (= $33,423.78 to us + $35,349.33 to applicants) with a range of $56,332.65 to $81,763.56. These calculations may overestimate the potential cost-savings if there are efficiency gains when potential applicants become more familiar with the process over time.

We do not have further information on the number of affected applicants or applications to monetize the total cost-savings associated with the final rule.

3. Potential Cost Savings to Insurers

Payors such as commercial or government drug-benefit programs who offer coverage of prescription drug products may experience cost savings. In addition, some of the cost savings to insurance administrators may likely come from not having to process the administrative claim for prescription drug products and future medical co-pays or future medical expenses when use of the nonprescription products increase adherence and improves health.

Changes in coverage for the drug product are in part considered a transfer because as insurance saves when a drug product is no longer covered consumers pay their portion in the post-switch scenario. However, this is not a zero-sum scenario where insurance simply transfers all of the burden to consumers; instead, prices after a switch may adjust to attract new consumers to pay out of pocket. These new consumers constitute about sixty percent of purchases (see appendix for details). Using MEPS data on nonprescription switches, we observe that out-of-pocket prices are on average the same before and after the switch, although there may be individual cases where the price increases or decreases.

Estimating the potential transfers and netting out any cost savings would require detailed payment data such as reimbursement rates from commercial insurance companies and government drug-benefit programs, as well as detailed information on different groups of consumers. Insurance claims do not capture data to estimate changes in payment from switching prescription to nonprescription drug products because as coverage drops the costs for noncovered drugs are no longer recorded.

We received comments, however, that further shed light on insurance coverage. For example, we received comments indicating that for some individuals with limited income, some Medicare Advantage and Medicaid plans include supplemental benefits that provide a regular allowance for nonprescription drug products related to their conditions. We also received comments that beneficiaries with Medicaid can obtain coverage when the nonprescription products are indicated by physicians. In general, based on nonprescription experience, we estimate that about forty percent of nonprescription drug purchases are from consumers who

548 transfer. Based on these comments, we assume the forty percent is an upper bound of such
549 transfers, but we have no further information to present a lower bound.[7]

550 *4. Summary of Benefits*

551 Table 4 shows the summary of per unit quantified benefits. Our primary estimate of the
552 potential reduction in access costs is $33.62 and a range of $0 to $67.23The reduction in access
553 costs includes the comparison of out-of-pocket costs, transportation costs, and time costs relative
554 to the baseline prescription-only scenario.

555 The potential cost savings from fewer meetings between us and industry are presented as
556 per application reductions. The primary estimate is $68,773.11 with a range of $56,332.65 to
557 $81,763.56. We do not calculate these benefits over time given the lack of information on the
558 number of potential applications, the probability of approval for each, and how often they would
559 occur per year over a ten-year horizon.

560 We also do not estimate potential cost savings to government-sponsored or commercial
561 insurers due to lack of reimbursement data. Estimating the potential transfers and netting out any
562 cost savings to insurers would require detailed payment data, such as reimbursement rates from
563 commercial insurance companies and government drug-benefit programs, as well as detailed
564 information on different groups of consumers.

565 Table 4. Summary of Potential Benefits and Cost Savings ($dollars 2023)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Reduction in Access Costs (per consumer)	$33.62	$0.00	$67.23
Reduction in meetings between FDA and industry (per application)	$68,773.11	$56,332.65	$81,763.56
Potential cost saving to insurers	NA	NA	NA

[7] Additional data sets would be needed if this analysis were to estimate these savings more broadly, including the portion paid by insurance, government or other payers.

Note: Numbers are rounded to nearest decimal. Because we have not projected the reduction in access costs to the national level, it is not appropriate to add the two rows in this table. (NA) means data not available for estimates. For example, we anticipate potential cost savings to insurers but lack data to estimate them.

F. Costs

In this section we present the costs of reading and understanding the rule. In the uncertainty section, we show how the rule could affect application development and application review costs if the rule encourages applications that will not occur without the rule or encourages applications to be submitted earlier than without the rule.

1. Reading and Understanding Costs

We expect potential applicants will incur one-time costs to read and understand the rule. To estimate these costs, we multiply the estimated hours to read and understand by the fully loaded hourly wage rates. Table **5** shows our estimates. We use hours to read and understand based on small and large firms by following HHS guidance.[8] For example, we estimate the lower bound as the average of three hours considering a mix of half small and half large firms. For example, for small firms, reading and understanding will take two hours if these firms find the complexity of the rule low, and about four hours for a large firm. For the upper bound we estimate an average of ten hours, considering that small firms that spend more time reading and understanding the rule will dedicate about seven hours and large firms about thirteen hours.

We use wages for operation managers (occupation code 11-3000) and legal occupations (occupation code 23-0000) from the Bureau of Labor Statistics-Occupational Employment Statistics for Pharmaceutical and Medicine Manufacturing.[9] The median wage for operation managers is $74.46, or $148.92 to reflect benefits and overhead costs. The median wage for legal

[8] Guidelines for Regulatory Impact Analysis. U.S. Department of Health and Human Services – May 2015 update.
[9] https://www.bls.gov/oes/current/naics4_325400.htm#11-0000

occupations workers is $103.50, or $207 to reflect benefits and overhead costs. The average of these fully loaded wages is $178. The resulting one-time cost estimate of reading and understanding the rule per potential applicant is $1,156.74 with a range of $533.88 to $1,779.60.

We do not aggregate these estimates to the industry level because the high uncertainty about the number of potential interested sponsors and because all estimates presented in this analysis, including benefits, are presented on a per case basis. For example, using the count of 2,350 pharmaceutical stakeholders from the 2017 economic census of Pharmaceutical and Medicine Manufacturers would yield an upper bound of $4.18 million ($1,779.60 multiplied by 2,350 manufacturers).[10] However, this upper bound is a gross overestimation of these costs. Based on the annual average approvals of nonprescription drug products, a more realistic number would likely resemble the count of interested sponsors in nonprescription markets of about three per year. Over a ten-year horizon of our primary estimates and about three sponsors per year, the resulting estimate would be $34,702.20 ($1,779.60 multiplied by 30 sponsors).

Table 5. One-Time Reading and Understanding Costs per Applicant ($ dollars 2023)

Item	Primary	Lower Bound	Upper Bound
Hours to Read and Understand	6.5	3.0	10.0
Hourly Wage	$177.96	$177.96	$177.96
One-Time Cost per Applicant	$1,156.74	$533.88	$1,779.60

Note: Cost is one-time.

G. Distributional Effects

For each nonprescription approval with an ACNU, insurers might experience cost savings if their coverage costs decrease because consumers who originally purchased the prescription drug product transfer to the nonprescription with an ACNU alternative.

[10] United States Census Bureau, U.S. Department of Commerce, Statistics of U.S. Businesses. Accessed June 2020, www.census.gov/programs-surveys/susb.html.

Retailers could gain marginal profits from sale of the product and from any marginal increase in foot-traffic at their stores from new consumers who would purchase the nonprescription drug product with an ACNU. However, retail pharmacies may also experience a small negative transfer from consumers switching from the prescription product to the nonprescription product if their profit margins are lower with the nonprescription product. We do not know if the balance of transfers will be a net positive or negative for retailers, but we anticipate this is not a major part of their transactions.

Other potential transfers, that we are not able to quantify, could include supply-chain transfers. For example, manufacturers that switch, partially or fully, to producing a nonprescription-ACNU product may reduce, or eliminate, the need for Pharmacy Benefit Managers. We expect that short-run transfers will differ from long-run transfers as the healthcare market and the retail market adjust. In addition, we do not have data to estimate a potential change in doctor visits due to the rule and potential related impacts.

H. International Effects

The final rule will allow any applicant, foreign or domestic, to apply for a nonprescription drug product with an ACNU. We do not expect international effects from the rule.

I. Uncertainty and Sensitivity Analysis

The rule will establish requirements for nonprescription products with an ACNU, and this could result in more approvals of NDAs and ANDAs. We show the average value consumers will get from one nonprescription product in a sensitivity scenario. Some consumers will be transfer consumers (consumers who switch from prescription to non-prescription with ACNU) and others new-to therapy (consumers not currently taking the medication). We also show

potential benefits to applicants. See appendix for full details on these calculations, including a graphical description of access costs using a demand-supply model.

In the main analysis, the quantified estimates including benefits from fewer meetings per applicants and costs from reading and understanding per applicant. We also estimated the potential reduction in access costs, but these estimates are per consumer per purchase and are not for comparison at the applicant-application level. In Table **6**, we present annualized benefits from fewer meetings minus annualized costs from reading and understanding the rule assuming one applicant but without assuming approval. The resulting net benefits from the main analysis will average $0.07 million and range from $0.05 million to $0.08 million.

In contrast to the main analysis, the sensitivity scenario shows the net benefits from assuming one application approved. In this scenario, we add the benefits to transfer consumers, new consumers, and applicants, and the cost savings from more efficient meetings with applicants. We also subtract application development costs, review costs, and reading and understanding costs. The result is $127.83 million in annualized primary net benefits using a 7-percent rate ranging from $125.89 million to $129.77 million. We annualize estimates over a 10-year horizon for a single application reviewed and approved. Using a 3-percent discount rate, the primary net benefits will average $129.16 million with a range of $127.50 million to $130.81 million. This sensitivity analysis shows that the net combined benefits to consumers and applicants will likely exceed one hundred million dollars per approval thus providing support for this rule. To assess the net benefits from more than one approval simply multiply these net benefits by the number of approvals. See the Technical Appendix for full estimation details.

Table 6. Annualized Net Benefits Comparison: Main Analysis Compared to Sensitivity Scenarios ($ millions 2023)

Scenario	Primary Estimate (7%)	Lower Estimate (7%)	Upper Estimate (7%)	Primary Estimate (3%)	Lower Estimate (3%)	Upper Estimate (3%)

Main Analysis (Fewer Meetings minus Reading Costs)	$0.07	$0.05	$0.08	$0.07	$0.05	$0.08
Sensitivity Scenario 1 (Net Benefits from One Approval)	$127.83	$125.89	$129.77	$129.16	$127.50	$130.81
Sensitivity Scenario 2 (Net Benefits from Six Approvals and 25 Post-marketing Reports)	$766.10	$754.61	$777.58	$774.05	$764.29	$783.82

Note: Numbers are rounded to nearest decimals. All estimates are annualized over a ten-year horizon. Net benefits include benefits, costs, and cost-savings.

The second sensitivity scenario in Table **6** shows the resulting annualized benefits when considering six approvals instead of one. These estimates reflect the same estimates as in the sensitivity scenario 1 multiplied by six approvals. The resulting primary estimates are $766.10 million using a 7-percent discount rate (ranging from $754.61 million to $777.58 million) and $774.05 million using a 3-percent discount rate (ranging from $764.29 million to $783.82 million). We also subtract the costs of 25 potential post-marketing reports per application to notify us of ACNU failures. To value the cost of these post-marketing reports, we use the cost of a medication error report from a 2019 ERG report as a proxy updated to 2023 dollars using the GDP deflator.[11] These estimates, rounded to the nearest dollar, range from about $475.64 to $701.53 and average about $588.59 per report.

J. Alternatives to the Rule

We identified the following plausible alternatives.

1. Retain Current Regulatory Framework

One alternative to the rule involves retaining the current regulatory framework. This alternative will hinder development of new nonprescription products with an ACNU. This

[11] From "Table 3-7. Medication Error Reporting—Labor hours and Unit Cost" on page 42 of the report.

alternative will impact the options available to consumers as well. In addition, this option has already created inefficiencies in the allocation of resources for industry and us in the form of multiple repetitive meetings.

2. Require Specific Technology or Conditions to Implement the ACNU

Another alternative would be to have a more stringent rule that would require the ACNUs to be operationalized in the same way for the reference product and for its potentially competing ANDAs. Some potential benefits of this alternative may include standardized ACNUs for both the reference product and potentially competing ANDAs so that consumers may avoid any confusion or inconvenience from choosing one product over another. Standardization of ACNUs may also help point-of-sale outlets when ACNUs involve any actions or technologies at these outlets. This alternative, however, would have some trade-offs as it would give less flexibility to applicants and potentially result in fewer applications submitted. The rule currently gives ANDA applicants flexibility regarding the way the ACNU will be operationalized if the ANDA's ACNU achieves the same purpose and the differences from the RLD are otherwise acceptable in an ANDA.

III. Final 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. The final rule will establish requirements for a nonprescription drug product with an ACNU. We anticipate that this rule will provide flexibility in the approval and application process for all applicants, large and small. We also anticipate that the rule will incentivize submission of applications from both small and large applicants.

Although small entities will incur the costs to develop and apply for a nonprescription drug product with an ACNU, this will occur when entities believe that the profits from the approval will exceed the costs of the application process. For those firms that conduct development and submission activities, the economic impact may be significant, but we do not anticipate that the number of small entities involved will be substantial. We estimate that the cost of reading and understanding the rule will be between 0.04 percent and 0.12 percent of gross receipts of the very small potential applicants in the affected industry. This analysis, as well as other sections in this document and the Preamble of the final rule, serves as the Final Regulatory Flexibility Analysis, as required by the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

Without knowing the size of the potential applicants of a nonprescription drug product with an ACNU under this rule, we only describe the distribution of potential applicants in Table 7. We use the North American Industry Classification System (NAICS) to identify industry groups potentially affected by the rule. We also use the NAICS codes to identify the Small Business Administration's (SBA) thresholds for small firms.[12] The Small Business Administration (SBA) considers any pharmaceutical preparation manufacturing firm (NAICS code 325412) with fewer than 1,250 employees as a small business. Because the U.S. Census Bureau data reports the employment differently than the SBA size standards tables, in this analysis, firms with fewer than 1,000 employees are small entities.

We use data from the 2017 Statistics of U.S. Businesses (SUSB) from the U.S. Census to identify the number of firms and their size by employment and by annual revenues.[13] The

[12] The SBA cutoffs are provided for the four subclassifications of NAICS code 3254, but not for the category as a whole.
[13] SUSB link: https://www.census.gov/data/tables/2017/econ/susb/2017-susb-annual.html

economic census occurs every 5 years and released 3 years after. For example, the 2017 census was released in 2020. Data on revenue are only collected for years ending in 2 and 7. The most recent economic census where revenue were collected was 2022. These revenue data, however, are not yet available until 2025. Thus, we continue using revenue data from 2017 and update dollar values to 2023 using the GDP deflator. These data show that the total count of Pharmaceutical Preparation Manufacturing (NAICS code 325412) is 1,280 establishments. Based on these data, about 76 percent, or 976, of establishments had fewer than 1,000 employees. Furthermore, these establishments account for about 13 percent of the total revenue for the industry.

Table 7. Distribution of Small Establishments by Employment Size and Revenue--2017 U.S. Economic Census, NAICS code 325412 ($ millions 2023)

Employment Size	Number of Establishments	Total Revenue ($ millions 2023)	Average Revenue Per Establishment ($ millions 2023)
01: Total	1,280	$ 189,025.70	$ 147.68
02: <5 employees	334	$ 479.11	$ 1.43
03: 5-9 employees	137	$ 465.72	$ 3.40
04:10-14 employees	76	$ 747.27	$ 9.83
05: 15-19 employees	37	$ 493.32	$ 13.33
06: <20 employees	584	$ 2,185.42	$ 3.74
07: 20-24 employees	27	$ 314.04	$ 11.63
08: 25-29 employees	22	$ 209.59	$ 9.53
09: 30-34 employees	26	$ 354.43	$ 13.63
10: 35-39 employees	20	$ 281.62	$ 14.08
11: 40-49 employees	31	$ 684.01	$ 22.06
12: 50-74 employees	37	$ 1,007.23	$ 27.22
13: 75-99 employees	31	$ 1,319.89	$ 42.58
14: 100-149 employees	46	$ 2,289.54	$ 49.77
15: 150-199 employees	28	$ 1,593.10	$ 56.90
16: 200-299 employees	42	$ 2,389.44	$ 56.89
17: 300-399 employees	18	$ 2,030.02	$ 112.78
18: 400-499 employees	14	$ 1,967.01	$ 140.50
19: <500 employees	926	$ 16,625.34	$ 17.95
20: 500-749 employees	28	$ 2,636.95	$ 94.18

21: 750-999 employees	22	$ 4,518.81	$ 205.40
22: 1,000-1,499 employees	23	$ 2,288.48	$ 99.50
23: 1,500-1,999 employees	18	$ 2,804.42	$ 155.80
25: 2,500-4,999 employees	86	$ 12,592.30	$ 146.42
26: 5,000+ employees	171	$ 145,728.63	$ 852.21

Source: 2017 U.S. Economic Census. The economic census occurs every 5 years and released 3 years after. For example, the 2017 census was released in 2020. The 2022 revenue data are not available until 2025. Dollar values updated from 2017 to 2023 using the GDP deflator.

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

In the cost section, we estimate that reading and understanding costs will range from about $533.88 to $1,779.60. The lower bound reflects our calculations for small entities. This includes time to read the rule and communicate it across their organizations. These costs are minor; they represent between 0.04 percent and 0.12 percent of gross receipts for the smallest establishment in this sector (establishments with 0 to 4 employees). We expect that only firms interested in applying for a nonprescription drug with an ACNU will dedicate the resources to read and understand the rule. In section C of the appendix of this analysis, we present the application development costs to show their potential scale should a firm decide to apply. We certify that the rule will not have a significant economic impact on a substantial number of small entities.

Although we show that the potential profits will outweigh these costs, the initial investment to develop an application could be relatively large. Potential small applicants without easy access to the necessary funds to develop an application could find it more challenging to apply than sponsors with more funds. We note, however, that the rule does not affect this distribution of potential applicants or the market conditions that currently exist in the review and approval process of nonprescription products without an ACNU.

C. Alternatives to Minimize the Burden on Small Entities

FDA provides application fees waiver provisions for small applicants submitting prescription drug applications; for more details, see the Prescription Drug User Fee Amendments (PDUFA)[14] and the Generic Drug User Fee Amendments (GDUFA).[15]

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V. Technical Appendix: Models, Inputs, and Assumptions for the Uncertainty and Sensitivity Analysis

A. Model of Consumer Benefits

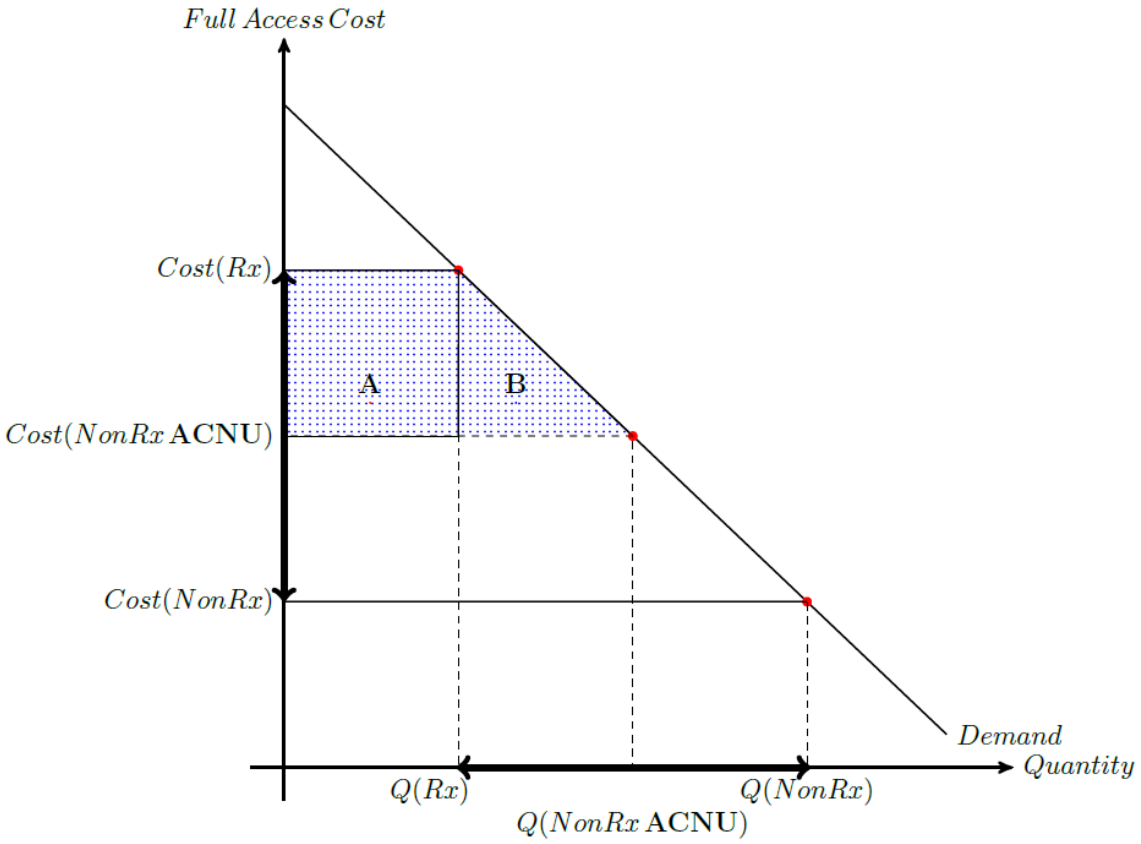
This appendix shows details of estimates we use in the uncertainty section of this analysis. For our sensitivity scenario, we estimate potential benefits to consumers and applicants and subtract potential development costs and review costs from one potential approval.

We estimate potential consumer benefits based on reduction in access costs relative to the baseline world with prescription-only products. Figure A1 shows access cost levels using three horizontal lines; a higher line represents higher access costs. The vertical axis represents access costs including costs beyond out-of-pocket such as transportation and time costs. The horizontal axis represents the number of total annual purchases estimated based on previous nonprescription switches. The demand curve shows the corresponding quantities consumed for every level of access costs.

We assume, the baseline market starts with consumers facing full costs to access a prescription product (Rx): Cost (Rx) and purchasing prescription quantity Q (Rx). Once a product is approved as a nonprescription drug product with an ACNU, consumers could experience a reduction in costs represented by the line Cost (NonRx-ACNU). The level of access cost could range between the Cost (Rx) and the Cost (NonRx) levels. This approach is flexible and allows for zero reduction in access costs in the range of possibilities.

Rectangle A represents benefits to transfer consumers defined as those who before the rule purchase the prescription-only drug product and after the rule purchase the corresponding nonprescription product with an ACNU. Triangle B represents the benefits of expanded access to new-to-therapy consumers (new consumers). As access costs decline, these two areas of benefits increase, and the opposite happens as access costs are closer to the upper bound of Cost (Rx).

Figure A1. Primary Estimates of Consumer Benefits from Approvals with ACNU Relative to Baseline Rx Products



Note: This figure ONLY shows consumer benefits; applicant benefits, and transfers must not be inferred from this figure because market price alone is not on the vertical axis. The horizontal axis measures quantity as the number of purchases. Rectangle (A) represents gains to consumers who switch from Rx to NonRx ACNU product. Triangle (B) represents gains to new-to-therapy consumers. Arrows on the axes represent that the ACNU scenario may range between the Rx and NonRx bounds.

1. Transfer Consumers

To estimate consumer benefits from consumers who switch from the prescription to the nonprescription purchase (rectangle A) we first calculate access-cost levels. Then, we multiply the difference in cost (vertical difference) by the expected change in number of purchases (horizontal difference).

We estimate access costs for the baseline, Rx scenario Cost (Rx), equal $79.38. This is estimated assuming one hour for transit and wait time (Temin 1992), valued using the hourly national average of $31.48 from the Bureau of Labor Statistics.[16] For the cost of transportation fare or gas, we use estimates from Pfoh et al. (2008), which equal about $18.06 when updated for inflation. We use national average co-pay per doctor visit from the Medical Expenditure Panel Survey (MEPS), which averages $29.84 across government-sponsored plans and commercial ones.[17] We assume that the change in the out-of-pocket per pack cost (e.g., bottle or box) is neutral and cancels out on average.[18] Adding all access costs results in a baseline of about $79.38 (= $31.48 in time costs + $18.06 in transportation expenses + $29.84 in copay for visit).[19] In Figure A1, this corresponds to the line Cost(Rx). If there is no reduction in access costs, the line Cost (NonRx ACNU) equals Cost (Rx) and areas A and B shrink to zero. This represents a lower bound on the effect of the rule.

By contrast, for the maximum reduction in access costs we estimate access costs of $12.15, which correspond to a level of costs comparable to a nonprescription case. We compare this estimate to the access costs in the baseline prescription case. We estimate $12.15 access costs assuming 15 minutes for transit and wait time (Temin 1992), valued using the hourly

[16] May 2023 wages available at: https://www.bls.gov/oes/current/oes_nat.htm#00-0000

[17] Estimated from 2016 reported co-pays for commercial plans and government-sponsored plans and updated for inflation to 2023 dollars using the GDP deflator. Available at: https://meps.ahrq.gov/data_stats/summ_tables/insr/national/series_1/2016/tif5.pdf and https://meps.ahrq.gov/data_stats/summ_tables/insr/national/series_3/2016/tiiif5.pdf

[18] We use data from the Medical Expenditure Panel Survey to estimate the change in out-of-pocket expenditures for a sample of drugs that switched from prescription to nonprescription status. We do so by comparing average expenditures before and after a marketing status switch. The data show that for the four markets examined (Lamisil, Pepcid, Mucinex, Plan B), there was an increase in out-of-pocket expenditures of $16 per package (bottle, box, etc.) on average. By contrast, we also observe that for four other markets (Prilosec, Miralax, Xenical, Prevacid) there was a decrease of about $12 per package (bottle, box, etc.). However, when aggregating all drugs, quantities purchased, and all years, the overall change is nearly zero. For this reason, we assume there is no change in out-of-pocket expenditures.

[19] Adding the out-of-pocket for the drug product would increase the total cost by about $30. Although the latter number may seem high, most of these products are initially branded, then nonprescription by the branded firm, and generic after that. For a deeper discussion on out-of-pocket trends, see Berndt and Newhouse (2012) p. 242.

national average of $31.48 from the Bureau of Labor Statistics. This results in a time-cost per event of $7.87 (= 0.25 hours x $31.48). For the cost of transportation fare or gas, we consider estimates from Temin (1992), which updated for inflation equals $4.28. In this case, transportation costs are significantly lower than in the prescription case as consumers may be able to shop for nonprescription products at more outlets and while doing other shopping activities. Although it is possible that some nonprescription purchases may result after visits to physicians, we assume that most nonprescription purchases are associated with no co-pay per doctor visit. We further assume that the change in out-of-pocket cost is neutral and cancels out on average, as in all the scenarios in this appendix. In Figure A1, this is line Cost (NonRx). Compared to the baseline of a prescription purchase, the cost reduction would be $67.23 (= $79.38 – $12.15).

For the primary estimate of the reduction in access costs we average the reduction in access costs between the upper and lower bound scenarios. We recognize that, without any data from drug approvals with an ACNU, assuming the primary estimate is the average between the lower and upper bounds is a reference point only. In Figure A1, this corresponds to the line Cost (NonRx ACNU). Compared to the baseline, the cost reduction would be $33.62 (= $79.38 – $45.76).

To calculate number of purchases, the horizontal measure in Figure A1, we use the Medical Expenditure Panel Survey (MEPS) to first get the percentage of consumers who switch from prescription to nonprescription purchases. MEPS data are collected directly from consumers' responses, and in the case of prescription medications, it is also verified with pharmacists and insurance claims when possible. We use six cases that experienced a nonprescription switch (Claritin, Prilosec, Zaditor, Zyrtec, Prevacid, Allegra) and estimate that at

most, 63.4 percent comes from new-to-therapy consumers and at least 36.6 percent from consumers who transfer. Next, using national sales data, from IQVIA (formerly known as IMS) for the same six cases, we estimate that on average about 6.2 million purchases occur annually per nonprescription product. Thus, combining these two pieces of information, the expected number of consumers who would switch per nonprescription product would average 2.3 million (= 36.6 percent of 6.2 million).

Multiplying changes in access costs (vertical line) by changes in nonprescription purchases (horizontal line), we calculate consumer benefits from consumers who will switch from a prescription drug product to the nonprescription drug product with an ACNU. This is the rectangle area (A) in Figure A1. For the primary scenario, the resulting estimate is $76.74 million (= $33.62 access cost reduction x 2.3 million purchases). For the low estimate scenario, the resulting estimate is $0 million (= $0 access cost reduction x 2.3 million purchases per nonprescription case per year, or by zero if consumers continue purchasing the prescription drug product.) For the upper-bound scenario, where the access costs for the nonprescription-ACNU would be like the access costs for nonprescription products without an ACNU, the resulting estimate is $153.48 million (= $79.38 access cost reduction x 2.3 million events).

Table A1.- Potential Benefits to Transfer Consumers ($ dollars 2023)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$79.38	$79.38	$79.38
Potential access costs	$45.76	$79.38	$12.15
Time cost per event	$19.68	$31.48	$7.87
Transportation cost per event	$11.17	$18.06	$4.28
Copay for visit	$14.92	$29.84	$0.00
Out-of-pocket per drug product purchase	same	same	same
Access cost reduction per purchase relative to baseline	$33.62	$0.00	$67.23
Number of purchases (million events)	2.28	2.28	2.28
Total cost savings per NonRx with an ACNU ($millions)	$76.74	$0.00	$153.48

Note: Numbers are rounded to the nearest decimal.

The estimated potential cost-savings using the set of assumptions and inputs are summarized in Table A1. We note that these estimates are based on a set of simplifying assumptions and a sample of products that may not be representative of what we may see with this rule.

2. New-to-Therapy Consumers

Next, we estimate incremental benefits from new-to-therapy consumers who would start purchasing a drug product when available as nonprescription with an ACNU (Triangle B in Figure A1). The access cost reduction estimates, the vertical measures, are the same as in our previous calculations for consumer benefits to transfer consumers.

We calculate the expected change in quantity of purchases, horizontal measures, as the difference between each scenario and the baseline Q (Rx). We use a linear demand model: Price = Intercept – Slope * Quantity. The reason for having a demand equation is to estimate the quantity of new-to-therapy in the mid-point between Rx and NonRx that is consistent with our access-cost estimates. We estimate this demand using two observations for access costs and two observations for the quantity of purchases. Thus, the slope is (Price Rx – Price NonRx) / (Quantity Rx – Quantity NonRx), or 0.0170 (= (79.38 – 12.15) / (2,283 – 6,231)). Prices are the same vertical measures we calculated for transfer consumers in the previous section. Quantities are average estimates, the horizontal measurers, we observe from IQVIA before and after a switch using data for six drug products that switched to nonprescription status (Claritin, Prilosec, Zaditor, Zyrtec, Prevacid, and Allegra). The intercept is Price + Slope*Quantity, or 118.25 (= 12.15 + 0.0170 x 2,283). Thus, the demand we derive is P = 118.25 - 0.0170Q, or Q = (118.25 - P) / 0.0170.

For each resulting point estimate of quantity, we separate new-to-therapy and transfer consumers based on the corresponding percentage we estimate from MEPS data. For the baseline Rx scenario, with access costs of $79.38, Q (Rx) = 2.3 million purchases, Q = (118.25 – 79.38) / 0.0170. In this baseline all consumers are transfer consumers and no new-to-therapy consumers. For Q (NonRx ACNU) the total purchases are 4.3 million purchases of which 1.97 million are new-to-therapy (= 4.3 million - 2.3 million baseline). For Q (NonRx) the total purchases are 6.2 million and 3.95 million are new-to-therapy (= 6.2 million - 2.3 million baseline).

Table A2.- Potential Benefits to New Consumers ($ dollars 2023)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$79.38	$79.38	$79.38
Potential access costs	$45.76	$79.38	$12.15
Time cost per event	$19.68	$31.48	$7.87
Transportation cost per event	$11.17	$18.06	$4.28
Copay for visit	$14.92	$29.84	$0.00
Out-of-pocket per drug product purchase	same	same	same
Access cost reduction per purchase relative to baseline	$33.62	$0.00	$67.23
Number of purchases (million events)	1.97	0.00	3.95
Total cost savings per NonRx with an ACNU ($millions)	$33.18	$0.00	$132.73

Note: Numbers calculated before rounding but are rounded in the table for presentation.

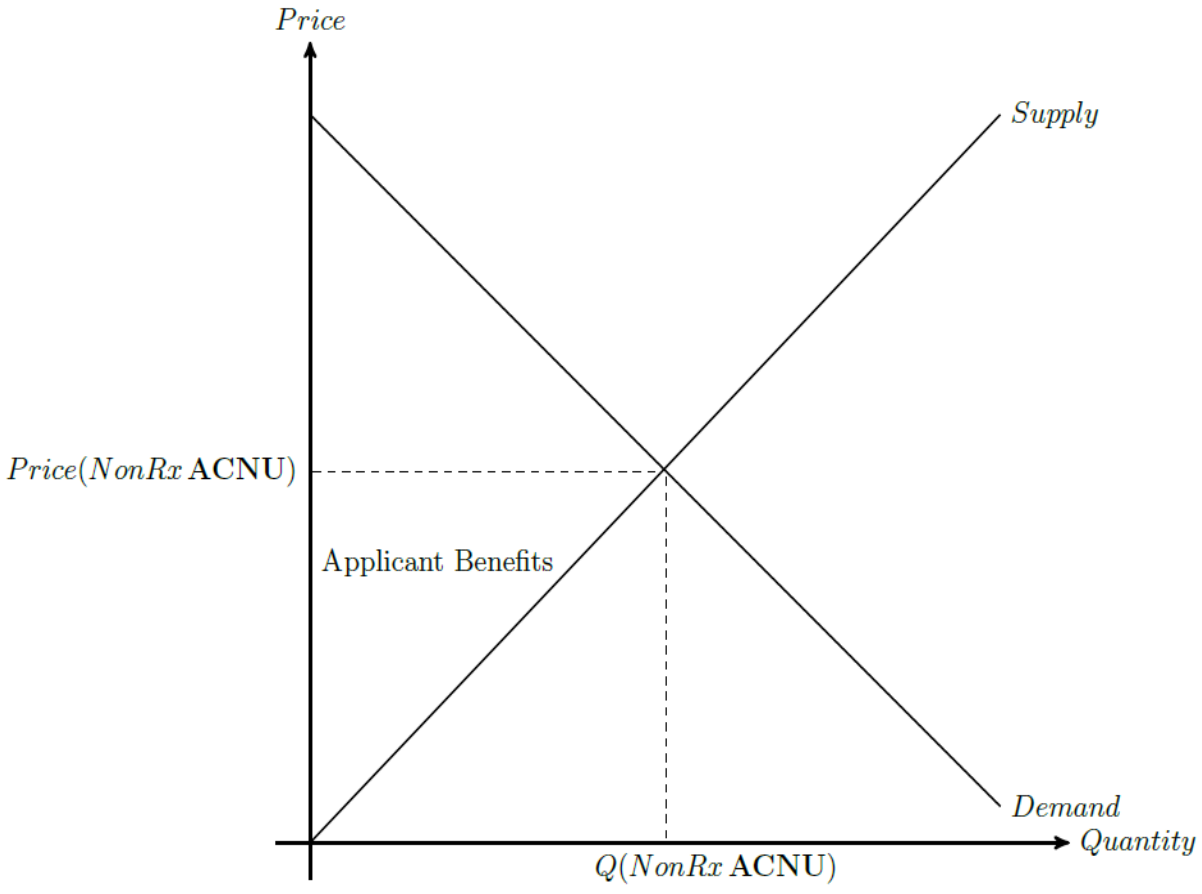
We estimate triangle B by multiplying the reduction in access costs (vertical measure) by the new-to-therapy estimates from the previous paragraph and divide by two. For our primary estimate, benefits to new-to-therapy consumers would equal $33.18 million (= ($33.62 cost reduction x 1.97 million purchases from new-to-therapy) / 2). For the low estimate, the benefits equal $0 million (= ($0 cost reduction x 0 million purchases from new-to-therapy) / 2). For the upper-bound estimate, where the access costs for the nonprescription-ACNU are as low as access costs of a nonprescription without the ACNU, the consumer benefits would equal $132.73 million (= ($67.23 cost reduction x 3.95 million purchases from new-to-therapy) / 2).

We summarized the estimated benefits in Table A2. We note that these estimates are based on the specific set of assumptions and data described above.

B. Model of Applicant Benefits

Applicants would consider whether to apply for a nonprescription product with an ACNU based on their expected benefits. The supply line in Figure A2 represents the quantities they will sell at each price level. Thus, applicant benefits would be the triangle area formed by the supply curve and the equilibrium price they receive above the minimum price they would be willing to sell their products for.

Figure A2. Illustration of Potential Applicant Benefits from a Nonprescription Product with an ACNU



To estimate applicant benefits we would need data or information to estimate the supply curve and the market equilibrium price. However, a simple way to approximate these benefits when a supply curve is not known is by calculating the rectangle of revenue from equilibrium price and quantities (P x Q) and dividing it by two; this calculates the area of a triangle. This approach assumes the supply curve is linear, has a constant slope, and begins at zero (i.e., some applicants would be willing to sell near marginal cost of production, and this cost is close to zero). This approach could overestimate benefits compared to when costs of production are relatively high.

In our analysis, we use revenue data from nonprescription switches without an ACNU. These data represent an upper bound of incremental revenue. We also present other estimates that reflect this uncertainty. Revenue data are from IQVIA, a provider of national pharmaceutical sales data, to measure applicants' revenue and estimate that every year nonprescription manufacturers get $112.02 million of additional annual revenue from switching a drug to nonprescription status. This number represents the aggregate incremental revenue from new consumers and consumers who switch from prescription to nonprescription purchases from six drug products that switched to nonprescription status (Allegra, Claritin, Prevacid, Prilosec, Zaditor, Zyrtec).

Thus, to measure the incremental increase in revenue we distinguish between consumers who transfer from the prescription market and new consumers. The effect on revenue depends on the pricing applicants set in the two markets and how consumers respond. We assume for simplicity that the profit reduction in the prescription market is, on average, balanced out by revenue gained in the nonprescription market from this group of consumers. Thus, incremental revenue comes from new consumers. Using MEPS data on nonprescription purchases, as for

consumer benefits, we estimate that up to 63.4 percent of all nonprescription purchases are from new-to-therapy consumers with a primary estimate of 46.4 percent that we derive from the demand equation above. The lower bound is zero as in the consumer benefits section; this scenario represents when there is not enough reduction in access costs to attract new consumers.

Using one half of the revenue, (P x Q / 2), and the expected new consumption estimates, for our primary calculation we estimate that a nonprescription drug product with an ACNU would generate about $25.97 million (= $112.02 million x 46.4 percent / 2). For the lower bound, we estimate incremental consumer benefits of $0 million (= $112.02 million x 0 percent new consumers / 2). For the upper bound, we estimate incremental consumer benefits of $35.49 million (= $112.02 million x 63.4 percent / 2). We note that these estimates are approximations for reference because of the simple but strong assumptions necessary to calculate them and because we use data for nonprescription products without an ACNU.

C. Potential ACNU Development and Post-approval Costs

In this section, we consider application development costs necessary for the applications that may result from this rule.

Based on our experience with review of nonprescription product applications and interactions with industry, we assume that core development costs, administrative effort, and labeling would account for about sixty to seventy percent of all costs to prepare application materials. We assume that costs related to the ACNU, such as development costs, implementation costs, and maintenance along with post-marketing and recordkeeping costs would account for the remaining thirty to forty percent of costs. ACNU development costs would likely include consumer studies added to core development studies common to nonprescription product applications.

We believe technology-based ACNU applications may need one or more of the following consumer studies:

- Human Factors Studies. These are infrequently performed for most nonprescription applications, and when they are performed, they are done on a small scale. These studies would be necessary to show the interactions between the consumer and the ACNU technology.

- Actual Use Studies. These studies would be more complex than traditional nonprescription applications due to the technology interaction. Longer study timeframes may also be required of up to 1 year (typical Actual Use studies, when required, are between 3-6 months).

- Self-Selection Studies. The number of these studies would likely not change, but their complexity or the nature of the study could increase.

- Label Comprehension Studies. This is the most common study performed for nonprescription drugs. The number of these studies would likely not change, but their complexity or the nature of the study could increase.

The rule would require applicants to submit a post-marketing report of ACNU failure. The rule would also require that applicants maintain for a period of 10 years records of all reports of ACNU failures and associated adverse drug experiences known to the applicant, including raw data and any correspondence relating to a report of ACNU failure. We lack data on the potential frequency of these reports and associated costs. For simplicity, we present cost-estimates of one report every year. We use the cost of a medication error report from a 2019 ERG report as a proxy updated to 2023 dollars using the GDP deflator.[20] These estimates, rounded to the nearest dollar, may range from about $475.64 to $701.53 and average about $588.59 per report. These estimates do not reflect any incremental cost of recordkeeping. It is likely that recordkeeping is a standard practice and that with electronic records the cost to applicants may be minimal or close to zero.

[20] From "Table 3-7. Medication Error Reporting—Labor hours and Unit Cost" on page 42 of the report.

For our primary estimate of development costs, we use $31.1 million for core development costs and about a markup of $16.2 million for ACNU-related cost per application for a total of $47.3 million. The $31.1 million is an estimate from our Center for Drug Evaluation and Research (CDER) based on feedback from industry on nonprescription drug product applications generally. We anticipate the additional markup to reflect a higher level of effort to develop ACNU materials.

For our lower bound estimate, we use $37.7 million as our estimate of development costs per approval (= $24.9 million for core development costs + $12.8 million for ACNU-related costs). Our upper-bound estimate of development costs for one application includes $37.3 million cost of developing all core nonprescription materials for an application, and about $19.6 million cost to develop and implement the ACNU. These costs combined amount to $56.9 million.

D. Review Costs

Because the rule could result in more applications, we also present our review costs for one application. We use review-costs estimates to process applications from the user fees under PDUFA's schedule of fees.[21] Our lower-bound is about $2.02 million for NDAs without clinical data. For our upper bound, we use $4.05 million for NDAs with clinical data; this scenario is for applications with more complex ACNU studies, although clinical data may not be required for nonprescription products with an ACNU. For the primary estimate, we use the average of these two costs, $3.04 million.

[21] https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/