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]

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

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. 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 0.14 percent of the gross receipts of very small applicants. Therefore, we propose to certify that the proposed rule, if finalized, would not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or

more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The proposed rule, if finalized, would establish for any applicant deciding to use this path the requirements for a nonprescription drug product with an additional condition for nonprescription use (ACNU). Compared to the traditional labeling paradigm of nonprescription drug products, this approved ACNU in addition to the labeling would ensure the appropriate self-selection, appropriate use, or both of a drug product. We expect this rule would expand consumer access to certain drug products in a nonprescription setting.

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 $26.7 dollars with a range of $0 to $53.4 dollars per consumer per purchase. We also quantify the value of the potential reduction in the number of repetitive meetings with applicants that would occur during the approval process. This estimate includes benefits to FDA and industry. Our primary estimate is $55,469 dollars per applicant with a range of $45,260 to $66,174 dollars. We do not monetize our estimates of benefits over a ten-year horizon because of the high uncertainty about number of applicants, applications, potential approvals, the number of purchases that might occur, and consumer preferences to switch products. However, we present estimates in the uncertainty section of this analysis. In addition, although private and government sponsored drug coverage plans would experience cost savings if their cost of coverage decline, we do not estimate such cost savings due to lack of data.

Although an applicant will incur the costs to develop and submit an application 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 over a ten-year horizon; we request comment or data on this.

Monetized costs include a one-time cost of reading and understanding the rule for those potentially interested in pursuing this path for their drug products. Using a 7-percent discount rate, the primary estimate, annualized over a ten-year horizon, equals $821 dollars with a range of $379 to $1,264. These annualized costs are the same using a 3-percent discount rate.

Government and private insurance payers may experience cost savings because the availability of nonprescription drug products with an ACNU may decrease future medical costs and the number of submitted insurance claims. For example, access to drug products under this new paradigm would allow consumers to treat medical conditions using nonprescription drug products with an ACNU without the supervision of a health care practitioner.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year							
	Annualized Quantified				2021			Quantified reduction in access costs per consumer purchase range from $0.0 to $53.40, and a primary estimate of $26.70
					2021			Quantified reduction in meetings

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
								between FDA and applicants range from $45,260 to $66,174 per applicant, and a primary estimate of $55,469
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.0	$0.0	$0.0	2021	7%	10 years	Reading and understanding one-time costs
		$0.0	$0.0	$0.0	2021	3%	10 years	
	Annualized Quantified							
	Qualitative							Interested firms would incur costs to develop and submit applications
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			Potential cost savings to government and private 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 would range from 0.04 percent to 0.14 percent of gross receipts. Wages: No estimated effect. Growth: No estimated effect.							

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II. Preliminary Regulatory Impact Analysis

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 healthcare practitioner licensed by law to administer such drugs. By contrast, nonprescription drugs do not require supervision by a healthcare practitioner in order to be used safely, provided certain conditions are met. 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 to enable 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 proposed rule would amend FDA's regulations to exempt a nonprescription drug product with an ACNU from the requirements for adequate directions for use.

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 nonprescription is commonly referred to as a prescription-to-nonprescription switch. To seek approval for a prescription-to-nonprescription switch, an applicant would conduct requisite

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

studies and submit 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 other human factor studies.

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

Starting in 2012, we held a public hearing and three expert workshops to solicit public input on expanding the approval of nonprescription drug products by requiring certain conditions of use. We issued draft guidance in July 2018 that describes innovative approaches that may be useful for applicants to consider in cases where Drug Facts Labeling described in 21 CFR 201.66 alone is not sufficient to ensure that a drug product can be used safely and effectively in a nonprescription setting.

This proposed rule, if finalized, would codify the application requirements, labeling requirements, and postmarketing reporting requirements for nonprescription drug products with an ACNU. In addition, the rule would 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 proposed rule clarifies that the ACNU would constitute a meaningful difference between the two drug products. The rule would allow a direct-to-nonprescription

pathway for nonprescription products with an ACNU (i.e., they would not necessarily need to be approved as prescription drugs first).

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

FDA's regulatory role in approving drugs arises from information asymmetry. For example, without approval, consumers would not know if drug products are safe and effective prior to using them. A second form of market distortion (government failure) arises as technology develops, innovation occurs, and regulations may need to adapt to such a change to allow markets to function. Thus, this rule is intended to establish requirements, including content and format requirements, for a nonprescription drug product with an ACNU. The regulation is also intended to 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.

Although the draft guidance encourages applicants to meet with FDA to discuss questions that arise during the development of a nonprescription drug product with an ACNU, we are pursuing this rulemaking to establish 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 requirements for a nonprescription drug product with an ACNU would 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, if finalized, would reduce or eliminate this burden for potential applicants and us.

C. Purpose of the Proposed Rule

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

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 any failures in the implementation of an ACNU.
5. Require labeling statements to alert consumers that the nonprescription drug product has an ACNU.

This rule would 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 health care practitioner when the applicant demonstrates and FDA determines that labeling alone is insufficient to ensure appropriate self-selection or appropriate actual use, or both. When labeling alone can sufficiently ensure appropriate selection and use of a nonprescription drug product, we would approve the drug only as a nonprescription drug product and would not approve it as a nonprescription drug product with an ACNU.

The proposed rule has the potential to broaden the types of drug products that could be approved as nonprescription. Approvals under the rule would 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 would remain as prescription-only drug products or, perhaps, not marketed at all. In addition, industry would continue requesting information on this topic on a case-by-case basis. The rule would 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 would treat.

E. Benefits

By establishing the 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.

However, we lack data or adequate information to monetize these potential benefits and cost-savings. In the sensitivity section we present estimates using assumptions regarding the number of applications we might receive, the number of purchases that might occur, and consumer preferences to switch products. We request comment or data on the potential benefits or cost-savings associated with this rule, as well as on any of the quantified benefits presented in this 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 proposed 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 would 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 would 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 version of a prescription drug that becomes available under the proposed rule, if finalized. We first estimate access costs for the baseline prescription scenario of $63.1. 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 $23.86 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 $15.3 when updated for inflation. We use national average co-pay per doctor visit from the Medical Expenditure Panel Survey (MEPS), which in 2016 averaged $24.[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.[5] Adding all of these

[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

[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 dollars 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 dollars 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.

access costs results in a baseline of about $63.1 dollars = $23.9 in time costs + $15.3 in transportation expenses + $24 in copay for visit.[6]

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

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$63.1	$63.1	$63.1
Potential access costs	$36.5	$63.1	$9.8
Time cost per event	$14.9	$23.9	$6.0
Transportation cost per event	$9.6	$15.3	$3.8
Copay for visit	$12.0	$24.0	$0.0
Out-of-pocket per purchase	same	same	same
Access cost reduction per purchase relative to baseline	$26.7	$0.0	$53.4

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 $23.9 hourly average wage. In column four, this estimate is 0.25 hours lost in transit and wait time multiplied by $23.9 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 estimate access costs of $9.8 = $6 in time costs + $3.8 in transportation expenses + $0 in copay for visit. Compared to the baseline, the maximum cost reduction would equal $53.4= $63.1 – $9.8. 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 pharmacists

[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.

interactions. For our primary estimate of the reduction in access costs we average the upper and lower reduction in access costs, which results in $26.7.

In the sensitivity analysis, we make simplifying assumptions about the number of purchases to present estimates of potential benefits of the proposed rule. We seek comments on the data or assumptions on this and other parts of the analysis.

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 before and after we issued the draft guidance. Based on this experience, we anticipate that the proposed rule, if finalized, would reduce resources equivalent to about 3 to 4 meetings per applicant. 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 $137.7 and calculate that our cost savings from eliminating these meetings would equal about $30 thousand (4 meetings x 55 hours per meeting x $137 fully-loaded hourly wage) per potential applicant. Similarly, we estimate the lower-bound cost savings to us would be about $22.6 thousand (3 meetings x 55 hours per meeting x $137 hourly wage). The primary estimate is about $26.3 thousand, the average of the upper and lower bound.

Table 3. Cost Savings from Fewer Meetings per Application

Item	Primary	Lower	Upper
Number of meetings that could be avoided per application	3.5	3	4
FDA hours per meeting	55	55	55
Fully-loaded wage FDA ($dollars)	$137.7	$137.7	$137.7
Cost to FDA ($ thousands)	$26.3	$22.6	$30.1
Applicant hours per meeting	55	55	55
Fully-loaded wage applicants ($dollars)	$147	$137.7	$155.6
Labor costs to applicants ($thousands)	$28.2	$22.7	$34.2
Transportation, lodging, and other expenses ($dollars)	$933.7	$0	$1,867.4
Cost to applicants ($thousands)	$29.2	$22.7	$36.1
Total reduction in meeting costs (FDA + applicants) ($thousands)	$55.5	$45.3	$66.2

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 mean hourly wage of $155.6 ($77.8 x 2 to account for overhead) from the Bureau of Labor Statistics occupational employment records for operations managers in the pharmaceutical industry (North American Industry Classification System (NAICS) 325400). We estimate an upper-bound cost savings per application of about $34.2 thousand (4 meetings x 55 hours per meeting x $155.6 mean wage per hour). In addition, we calculate cost savings from avoided lodging and transportation of $1,867.4 for all four meetings (4 meetings x $466 lodging and transportation per meeting). The combined upper-bound cost savings per application equals $36.1 thousand.

For our lower-bound estimate, we use the median hourly wage of $137.62 ($68.81 x 2) which is lower than the mean wage of $155.62. Thus, our lower-bound estimate equals about $22.7 thousand (3 meetings x 55 hours x $137.62 wage). In this case, we do not add lodging and

transportation because we assume that applicants would submit letters or call us instead of meeting in person.

Our primary estimate equals about $28.2 thousand (3.5 meetings x 55 hours per meeting x $147 average wage per hour between upper and lower wage). In addition, we calculate cost savings from avoided lodging and transportation of $933.7, average between lower and upper bounds for this item. The combined primary cost savings per application to the applicant would be about $29 thousand.

Adding these benefits for potential applicants and us, on average, we estimate cost-savings from fewer meetings costs per application would equal about $55 thousand ($26.3 thousand to us + $29.2 thousand to applicants) and would range from about $45 thousand to about $66 thousand. These estimates may overestimate the potential cost-savings if there are efficiency gains when potential applicants become more familiarized with the process over time.

We do not have information on the number of affected applicants or applications to monetize the total cost-savings associated with the proposed rule, if finalized. We seek data or comment on our estimates.

3. Potential Cost Savings to Insurers

Payors such as private insurers or government drug-benefit programs who offer coverage of prescription drug products would experience cost savings if their coverage costs for such drugs decrease when consumers who originally purchase the prescription drug product transfer to a nonprescription drug product with an ACNU. Although we can estimate the number of potential transfer consumers, estimating the potential cost savings, however, requires payment data such as reimbursement rates from private insurance companies and government drug-benefit

programs. We lack access to those data and request comment on these potential cost savings to insurers and any other potential cost savings not mentioned here.

4. Summary of Benefits

Table 4 shows the summary of per unit quantified benefits. The potential reduction in access costs are presented as per customer per purchase reductions. The potential cost savings from fewer meetings between us and industry are presented as per application reductions. We do not calculate these benefits over time given the lack of information on the number of potential applications, the probability of approval for each, and how often they would occur per year over a ten-year horizon. In addition, we do not estimate potential cost savings to private or public insurers due to lack of reimbursement data.

Table 4. Summary of Potential Benefits and Cost Savings ($dollars 2021)

Item	Primary Estimate	Lower Estimate	Upper Estimate
Reduction in Access Costs (per consumer)	$26.7	$0	$53.4
Reduction in meetings between FDA and industry (per application)	$55,469.4	$45,259.9	$66,173.9
Potential cost saving to insurers	NA	NA	NA

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 would 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 would 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.[7] For example, we estimate the lower bound considering that for small firms, reading and understanding would take two hours if these firms find the complexity of the rule low and about four hours for a large firm; the average is three hours considering a mix of half small and half large firms. Similarly, for the upper bound, we consider that small firms that spend more time reading and understanding the rule dedicate about seven hours and large firms about thirteen hours; the average is ten hours. We use wages for operation managers and legal occupations from the Bureau of Labor Statistics-Occupational Employment Statistics for Pharmaceutical and Medicine Manufacturing.[8] The median wages for operation managers are $59.4 (doubled to $118.8 to reflect benefits and overhead costs) and $66.96 for legal occupations (doubled to $133.92 to reflect benefits and overhead costs). The average fully-loaded wage, therefore, is $126.4. The resulting one-time cost estimates of reading and understanding the rule per potential applicant are $821.3 dollars and would range from $379.1 to $1,263.6 dollars.

Table 5. One-Time Reading and Understanding Annual Costs ($ dollars)

Item	Primary	Lower Bound	Upper Bound
Hours to Read and Understand	6.5	3.0	10.0
Hourly Wage	$126.4	$126.4	$126.4
One-Time Cost per Applicant	$821.3	$379.1	$1,263.6

Note: Cost is one-time.

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

G. Distributional Effects

With 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. We request comment on any other potential cost savings or transfers.

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 would be on net positive or negative for retailers, but we anticipate this is not a major part of their transactions. We request comment on these potential transfers.

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 would differ from long-run transfers as the healthcare market and the retail market adjust. We request comment on potential transfers.

In addition, we do not have data to estimate potential change in doctor visits due to the rule, and potential related impacts. We seek comments or data on this topic.

H. International Effects

The proposed rule would allow any applicant, foreign or domestic, to apply for a nonprescription drug product with an ACNU. There are no international effects expected from the rule.

I. Uncertainty and Sensitivity Analysis

The rule would 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 would get from one nonprescription product in a sensitivity scenario. Some consumers would 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.

In Table 6 of the benefits section, we presented annualized benefits from fewer meetings minus annualized costs from reading and understanding the rule assuming there is one applicant with one approved application. These net benefits from the main analysis would range from $0.04 million to $0.07 million.

The sensitivity scenario shows the net benefits adding benefits to transfer consumers, new consumers, and applicants, and cost savings from more efficient meetings with applicants. We also subtract application development costs, review costs, and reading and understanding costs. The result is $100.5 million in annualized primary net benefits using a 7-percent rate ranging from $98.7 million to $102.2 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 would be $104.6 million ranging from $105.4 million to $103.8 million. See the Technical Appendix for estimation details.

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

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)	$0.05	$0.04	$0.07	$0.05	$0.04	$0.06
Sensitivity Scenario (Net Benefits from One Approval)	$100.5	$98.7	$102.2	$104.6	$105.4	$103.8

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

J. Alternatives to the Proposed Rule

We identified the following plausible alternatives. We request comments on how flexible or restrictive the ACNU should be depending on potential drug products that could switch to nonprescription status with an ACNU to help inform this economic analysis.

1. Retain Current Regulatory Framework

One alternative to the rule would be to retain the current regulatory framework. This alternative would hinder development of new nonprescription products with an ACNU. This

option would 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.

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 competing ANDAs. However, this alternative 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 would be operationalized as long as the different way to operationalize the ANDA's ACNU achieves the same purpose as the ACNU for its RLD and the differences from the RLD are otherwise acceptable in an ANDA.

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The proposed rule would establish requirements for a nonprescription drug product with an ACNU. We anticipate that this proposed rule, if finalized, would provide flexibility in the approval and application process for all applicants, large and small. We also anticipate that the rule would incentivize submission of applications from both small and large applicants.

Although small entities would incur the costs to develop and submit an application for a nonprescription drug product with an ACNU, this would 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 would be between 0.04 percent and 0.14 percent of gross receipts of the very small potential applicants in the affected industry. Thus, we propose to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities. We seek comment or data on this estimate and proposal. This analysis, as well as other sections in this document, serves as the Initial 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. 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 US 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. Based on the 2012 Economic Census data, about 98 percent of establishments had fewer than 1,000 employees. Furthermore, these establishments account for about 60 percent of the total value added (revenue minus costs of production) for the industry. The value added per small firm ranges from just under $1 million to $389 million with an average of about $100 million. We welcome comments on the impact of this rule on small firms.

Table 7. Distribution of Small Firms by Employment Size and Value Added (2012 US Economic Census, NAICS code 325412)

Firms by Number of Employees	Number Firms	Percent of Firms	Value Added ($millions)	Percent of Total Value Added	Average Value Added per Firm ($millions)
All	1165		$91,553.4		$78.6
Small		98.5%		60.1%	
0 to 4	349		$324.9		$0.9
5 to 9	138		$268.8		$1.9
10 to 19	136		$600.5		$4.4
20 to 49	193		$1,494.6		$7.7
50 to 99	102		$2,364.2		$23.2
100 to 249	105		$15,057.9		$143.4
250 to 499	89		$21,287.1		$239.2
500 to 999	35		$13,638.5		$389.7
Large		1.5%		39.9%	
1,000 to 2,499	12		$14,315.4		$1,193.0
2,500 or more	6		$22,201.5		$3,700.3

Source: 2012 US Economic Census. The economic census occurs every 5 years and released 3 years after. For example, the 2017 census is expected to be released in 2020. Value added is gross revenue minus costs of production. We use value added because some categories do not have revenue data.

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

In the cost section, we estimate that reading and understanding costs would range from about $379.1 to $1,264.6 dollars. The lower bound reflects our calculations for small entities. This includes time to read the rule and communicate it across their organization. These costs are minor; they represent between 0.04 percent and 0.14 percent of gross receipts for the smallest entities in this sector (entities with 0 to 4 employees). We expect that only firms interested in submitting an application for a nonprescription drug with an ACNU would dedicate the resources to read and understand the rule. In the uncertainty section in the appendix of this analysis, we also presented the application development costs. Although we show that the

potential profits would 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. However, we request comments on the potential effect of the rule on small applicants.

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)[9] and the Generic Drug User Fee Amendments (GDUFA)[10]. We request comments on what additional flexibilities would be relevant to small applicants.

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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.

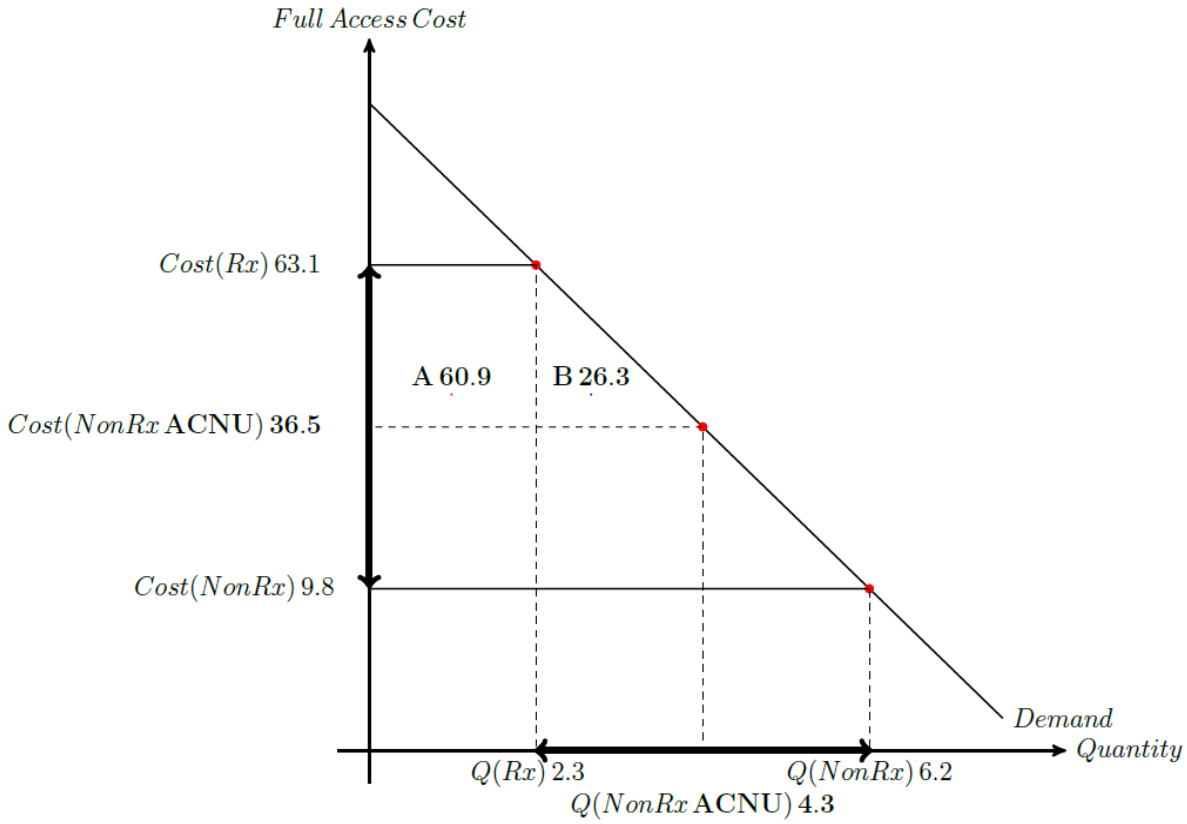
We estimate potential consumer benefits based on reduction in access costs relative to the baseline world with prescription-only products. Figure A1 shows access cost levels using three horizontal lines; a higher line represents higher access costs. The vertical axis represents access costs including costs beyond out-of-pocket such as transportation and time costs. The horizontal axis represents the number of total annual purchases. 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 line Cost (NonRx-ACNU). The level of access cost could range between the Cost (Rx) and the Cost (NonRx). 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 or switch to 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, 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 $63.1 dollars. This is estimated assuming one hour for transit and wait time (Temin 1992), valued using the hourly national average of $23.9 from the Bureau of Labor Statistics.[11] For the cost of transportation fare or gas, we use estimates from Pfoh et al. (2008), which equal about $15.3 when updated for inflation. We use national average co-pay per doctor visit from the Medical Expenditure Panel Survey (MEPS), which in 2016 averaged $24.[12] 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.[13] Adding all access costs results in a baseline of about $63.1 dollars = $23.9 in time costs + $15.3 in transportation expenses + $24 in copay for visit.[14] 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 would represent a lower bound on the effect of the rule.

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

[12] 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

[13] 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 dollars 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 dollars 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.

[14] 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.

582 By contrast, for the maximum reduction in access costs we estimate access costs of $9.8,
583 which correspond to a level of costs comparable to a nonprescription case. We compare this
584 estimate to the access costs in the baseline prescription case. We estimate $9.8 access costs
585 assuming 15 minutes for transit and wait time (Temin 1992), valued using the hourly national
586 average of $23.9 from the Bureau of Labor Statistics. This results in a time-cost per event of $6
587 (=0.25 hours multiplied by $23.9). For the cost of transportation fare or gas, we consider
588 estimates from Pfoh et al. (2008), which we adapt and update for inflation to form a range from
589 $0 to $15.3. Although we consider $0 to be a reasonable lower bound, we use one-quarter
590 relative to the upper bound instead, or $3.8 (=$15.3 divided by 4). In this case, transportation
591 costs are significantly lower than in the prescription case as consumers may be able to shop for
592 nonprescription products at more outlets and while doing other shopping activities. We further
593 assume that the majority of nonprescription purchases are associated with no co-pay per doctor
594 visit. Although, it is possible that some nonprescription purchases may result after visits to
595 physicians. We assume that the change in out-of-pocket cost is neutral and cancels out on
596 average. In summary, access costs for the nonprescription case are $6 time-costs + $3.8
597 transportation expenses + $0 in copay for visit. In Figure A1, this is line Cost (NonRx).
598 Compared to the baseline of a prescription purchase, the cost reduction would be $53.4= $63.1 –
599 $9.8.
600 For the primary estimate of the reduction in access costs we average the reduction in
601 access costs between the upper and lower bound scenarios. We recognize that, without any data
602 from drug approvals with an ACNU, assuming the primary estimate is the average between the
603 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 $26.7 = $63.1 – $36.5. We welcome comments on our assumptions and estimates.

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 would 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 $60.9 million = $36.5 access cost reduction multiplied by 2.3 million purchases. For the low estimate scenario, the resulting estimate is $0 million = $0 access cost reduction multiplied by 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 $121.8 million =$54.7 access cost reduction multiplied by 2.3 million events.

Table A1.- Potential Benefits to Transfer Consumers

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$63.1	$63.1	$63.1
Potential access costs	$36.5	$63.1	$9.8
Time cost per event	$14.9	$23.9	$6
Transportation cost per event	$9.6	$15.3	$3.8
Copay for visit	$12.0	$24.0	$0
Out-of-pocket per drug product purchase	same	same	same
Access cost reduction per purchase relative to baseline	$26.7	$0	$53.4
Number of purchases (million events)	2.3	2.3	2.3
Total cost savings per NonRx with an ACNU ($millions)	$60.9	$0	$121.8

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 if this rule is finalized. We seek comments on the assumptions, the methodology or other information used in this analysis.

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: 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 0.0135 = (63.14 – 9.79)/ (2283 - 6231). 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 93.99 = 63.14 + 0.0135*2,283. Thus, the demand we derive is P=93.99 - 0.0135Q, or Q= (93.99 -P)/0.0135.

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 $63.14, Q (Rx) = 2.3 million purchases, Q= (93.99 - 63.14)/0.0135. In this baseline all consumers are transfer consumers, that is there are no new-to-therapy consumers. For Q (NonRx ACNU) the total purchases are 4.3 million purchases of which 1.974 million are new-to-therapy (4.3 million - 2.3 million baseline). For Q (NonRx) the total purchases are 6.2 million and 3.9 million are new-to-therapy (6.2 million - 2.3 million baseline).

Table A2.- Potential Benefits to New Consumers

Item	Primary Estimate	Lower Estimate	Upper Estimate
Baseline access costs	$63.1	$63.1	$63.1
Potential access costs	$36.5	$63.1	$9.8
Time cost per event	$14.9	$23.9	$6
Transportation cost per event	$9.6	$15.3	$3.8
Copay for visit	$12.0	$24.0	$0
Out-of-pocket per drug product purchase	same	same	same
Access cost reduction per purchase relative to baseline	$26.7	$0	$53.4
Number of purchases (million events)	1.9	0	3.9
Total cost savings per NonRx with an ACNU ($millions)	$26.3	$0	$105.3

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

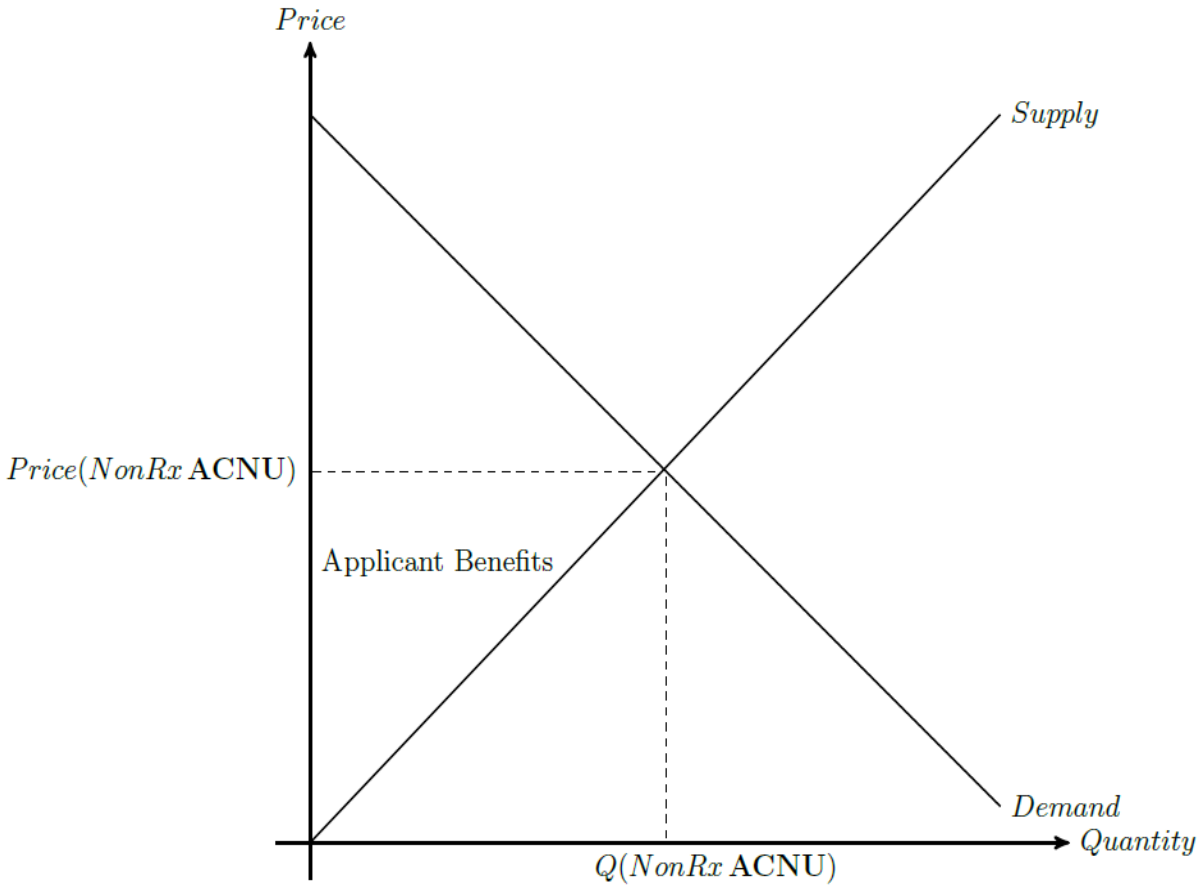
We estimate triangle B by multiplying the reduction in access costs (vertical measure) by the new-to-therapy estimates from the previous paragraph and divide by two. For our primary estimate, benefits to new-to-therapy consumers would be $26.3 million= ($26.7 cost reduction x 1.9 million purchases from new-to-therapy) ÷ 2. For the low estimate, the benefits would be zero 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 would be as low as access costs of a nonprescription without the ACNU, the consumer benefit would be $105.3 million= ($53.4 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. We seek data or comments on this analysis.

B. Model of Applicant Benefits

Applicants would consider whether to submit an application for a nonprescription product with an ACNU based on their expected benefits. The supply line in Figure A2 represents the quantities they would be willing to 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.

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 it when a supply curve is not known is by calculating the rectangle of revenue from equilibrium price and

quantities (P*Q) and dividing it by two; this calculates a triangle area. This approach assumes the supply curve is linear, has a constant slope, and begins at zero (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 $90 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 would 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 who do not purchase the drug product when the drug product is only available by a prescription from a healthcare practitioner. 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*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 $20.9 million = $90 million/2 x 46.4 percent. For the lower bound, we estimate that incremental consumer benefits would be $0 million =$90 million/2 x 0 percent. For the upper bound, we estimate that incremental consumer benefits would be $28.5 million = $90 million/2 x 63.4 percent. 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 if the rule is finalized.

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 welcome comments on the potential ACNU development costs as they could range from paper questionnaires to technology-driven screening devices and other technologies. 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 report post-market failures in implementing ACNUs and solutions for addressing them. The rule would also require that applicants maintain for a period of 10 years records of all reports of failures in implementation of an ACNU and associated adverse events known to the applicant, including raw data and any correspondence relating to a report of a failure in implementation of an ACNU.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.[15] These estimates, rounded to the nearest dollar, may range from about $389 to $574 dollars and average about $482 dollars per report. These estimates do not reflect any incremental cost of recordkeeping. It is likely that recordkeeping is a standard practice and that with

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

electronic records the cost to applicants may be minimal or close to zero. However, we request comments from potential applicants regarding recordkeeping costs.

For our primary estimate of development costs, we use $25 million for core development costs and about a markup of $15 million for ACNU-related cost per application for a total of $40 million cost. The $25 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 $15 million to reflect a higher level of effort to develop ACNU materials that may fall within thirty to forty percent of the entire cost.

For our lower bound estimate, we use $31.2 million as our estimate of development costs per approval ($20 million for core development costs and $11.2 million for ACNU-related costs). Our upper-bound estimate of development costs for one application includes $30 million cost of developing all core nonprescription materials for an application, and about $18 million cost to develop and implement. We further expect about $0.7 million for maintenance of the ACNU. These costs combined amount to $48.7 million.

We request comment or data related to this analysis.

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 2018.[16] Our lower-bound is about $1.2 million for NDAs without clinical data. For our upper bound, we use $2.4 million for NDAs with clinical data; this scenario is for applications with more complex ACNU studies, although clinical data may not be required

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

for nonprescription products with an ACNU. For the primary estimate, we use the average of these two costs, $1.8 million.