DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Regulations on Fixed-combination and Co-packaged Drugs: Applications for Approval and Combinations of Active Ingredients under Consideration for Inclusion in an Over-the-Counter Monograph; Proposed Rule

Docket No. FDA-2015-N-1260

Preliminary Regulatory Impact Analysis
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I. Preliminary Regulatory Impact Analysis

A. Introduction and Summary

1. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed requirements will have minimal economic impact of small entities (the unit cost of a waiver as a percent of the average of value of sales for a typical firm would be small—less than 0.15 percent of average sales for firms with 10-49 workers and even smaller for other small-size firms), the Agency anticipates that the proposed rule will not have a significant economic impact on a substantial number of small entities, and seeks comments on its Initial Regulatory Flexibility Analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the

expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

2. Summary

The proposed rule would harmonize the requirements for prescription and over-the-counter (OTC) fixed-combination and co-packaged drugs and clarify the types of studies needed for approval of these products. Although we are unable to quantify or monetize all of the benefits, harmonizing and clarifying current policy would result in benefits to industry as there would be less uncertainty surrounding the requirements for approval of the affected products. This may in turn incentivize the development of new products. We estimated benefits associated with reduction in preparation and review time of information that would not be necessary if the proposed rule were in effect. Estimated annual benefits range between $651,891 and $977,836.

Because the proposed requirements would codify current policy regarding the review of the affected products, there are no costs associated with this proposed requirement. However, the proposed rule would also create a provision under which sponsors can apply for a waiver when certain conditions are met. This proposed provision is a new requirement and would result in costs. Estimated annual costs of preparation and review of the proposed waiver range between $101,858 and $152,787.

The estimated annual benefits and costs are summarized in table 1 below.

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

Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized (millions $/year)	$0.815	$0.652	$0.978	2012	7%	2014-33	
	$0.815	$0.652	$0.978	2012	3%	2014-33	
Annualized Quantified					7%	2014-33	
					3%	2014-33	
Qualitative	Additional benefits may arise for sponsors who may incur development costs that could be prevented by clarifying the requirements of the products covered by the proposed rule.						
Costs							
Annualized Monetized (millions $/year)	$0.127	$0.102	$0.153	2012	7%	2014-33	
	$0.127	$0.102	$0.153	2012	3%	2014-33	Based on 10-15 waivers per year.
Annualized Quantified	None estimated.						
Qualitative	None estimated.						
Transfers							
Federal Annualized Monetized (millions $/year)	None estimated						
Other Annualized Monetized (millions $/year)	None estimated.						
Effects							
State, Local or Tribal Gov't	None						
Small Business	Based on the analysis small business entities covered by the proposed rule could incur costs of $6,701 per waiver or up to 0.15 percent of average annual sales for entities with 10-49 employees and even smaller for all other firms.						
Wages	No estimated effect.						
Growth	No estimated effect.						

B. Need for Regulation

One of the main objectives of the proposed rule is to harmonize the terminology and requirements for prescription and over-the-counter (OTC) fixed-combination and co-packaged drugs. The existing regulations cover prescription fixed-combination drugs (current 300.50) and combinations of active ingredients under consideration for inclusion in an over-the-counter (OTC) monograph (current 330.10(a)(4)(iv)), but they use different language for requirements that FDA has interpreted to be the same. For example, section 330.10(a)(4)(iv) refers to OTC combinations of "active ingredients" rather than "components" as is used in the prescription fixed-combination drug regulations; however, FDA has interpreted "component" in 300.50 to mean "active ingredient." (Other examples can be found in the preamble to this proposed rule.)

Although current 300.50 does not explicitly state that its requirements apply to co-packaged drugs, it has been the Agency's longstanding policy to apply these requirements to co-packaged drugs.[1] FDA has been reviewing applications of co-packaged drugs on a case-by-case basis by applying the statutory standards for safety and effectiveness as well as other applicable regulations for new drugs. The lack of specificity on approval requirements for co-packaged products result in products being marketed with implied claims that are not supported by scientific evidence.

Most approved drugs contain a single active ingredient that has been demonstrated to be safe and effective in treating a particular disease or condition. There are, however, combinations that would provide greater effectiveness than either ingredient alone but for which it would be

[1] Currently there are some types of OTC drug products marketed together (e.g., in the same package or shrink-wrapped together) as a "travel" or "convenience" kit or as a "value" pack, but the labeling does not state that the drug products/active ingredients are intended to be used together for a common or related therapeutic purpose. For these types of products, we generally do not require compliance with the fixed-combination requirements. Under the proposed rule, such products are not included with the definition of co-packaged product and therefore would not be subject to the rule.

infeasible (medically, or prohibitively costly) or unethical to meet the requirements of this proposed rule. One example where it would be unethical would be where randomizing the study drug could deny therapy that could reduce the risk of death or a major morbidity endpoint. An example of an infeasible case would be the conduct of a study for traditional botanical products that have so many ingredients that would make the study difficulty and costly. Another objective of the proposed rule is to include a provision specifying the types of products for which applicants or interested persons could apply for a waiver of some or all of the proposed requirements (proposed 300.53).[2] For instance, sponsors of products composed of or derived from multiple raw materials (e.g., two or more parts of a single plant species or from multiple species) that have a long history of use in traditional medicine, and which involve more extensive and lengthy clinical testing than is likely to be commercially feasible for such products, could apply for a waiver. In addition, sponsors of certain allergenic patch tests would also qualify for waivers.

The proposed rule would clarify and make explicit the requirements and conditions for approval of prescription and OTC drugs and biologics covered by the rule. This could result in improvements in the quality of information that FDA receives for review decisions. By clearly specifying the types of products that require studies to support an application or submission, there could be a reduction in the uncertainty or information needed for applicants or interested parties to develop and market innovative products. In addition, there could also be a reduction in FDA regulatory burden.

Because the proposed requirements are already implemented, we do not anticipate costs associated with the new provision that explicitly adds the requirements for applicants of co-

[2] This proposed requirement does not exempt approved waiver holders of all other applicable requirements.

packaged products. However, we anticipate costs arising from the new provision to implement a waiver for those applicants or interested parties who apply for a waiver.

C. Benefits of the Proposed Rule

Clearly specifying and harmonizing the requirements for fixed-combination and co-packaged products could reduce some of the unnecessary reporting by manufacturers and regulatory burden on FDA. Although some sponsors consult with FDA prior to the development of clinical trials or submission of a New Drug Application (NDA), not all sponsors do. Based on FDA experience, we estimate that there could be between 10 and 15 requests for waivers each year. Assuming that all of these submissions require more preparation and review than the proposed waiver, we can estimate some benefits associated with this provision. Using a sample of NDA approvals for the period 2007-2012, we determined that the minimum FDA review time for an NDA was 1 month (or 160 hours). We use this measure as an estimate of the time it would take FDA to review a package that contains more information than what would be needed if the sponsor met the requirements for a waiver.[3] We further assume that preparation time for the sponsors is twice the number of FDA review time, 320 hours. These hours are allocated between a scientist (25 percent, or 80 hours) and a regulatory affairs manager (75 percent, or 240 hours). FDA welcomes public comment on the accuracy of our assumptions regarding total sponsor preparation time, the allocation of hours across occupations, and the types of occupations included in the analysis.

Hours for a regulatory affairs manager are valued using the average hourly rate for

[3] This estimate is a lower-bound measure of benefits. Approval data between 2007 and 2012 indicate that the median approval time is ten months.

Medical and Health Services Managers (standard occupational classification code, SOC, 119111) in Pharmaceutical and Medicine manufacturing (North American Industry Classification System, NAICS, 325400) reported by the Bureau of Labor Statistics (BLS) May 2012 Occupational Employment Statistics (Ref. 1). The hourly wage rate for a regulatory affairs manager, adjusting for benefits and overhead is $136.74. The hours for a scientist are valued using the average hourly wage rate for Natural Sciences Managers (SOC 119121) in the pharmaceutical and medicine manufacturing industry as reported by the BLS (Ref. 1). The estimated hourly wage rate for a scientist is $125.84, adjusting for benefits and overhead. Finally, the annual cost of an FDA FTE is approximately, $289,956, which translates into an hourly wage rate of $139.40 (($289,956/52)*40).

The total cost savings associated with preparation and review time are calculated by multiplying the number of hours by the cost of labor. The estimated unit cost savings for FDA is estimated at $22,304 (160 hours * $139.40) per review. Similarly, for industry, the estimated per submission cost savings are estimated at $10,067 (320*0.25*$125.84) for scientist labor hours and $32,818 for regulatory affairs manager labor hours (320*0.75*$136.74). Adding these two estimates, the cost savings for sponsors is $42,885 ($10,067 + $32,818) per submission.

Summing over the estimated 10-15 submissions, the total cost savings for industry are estimated between $428,848 (10*$42,885) and $643,272 (15*$42,885). Total cost savings for FDA would be between $223,043 (10*$22,304) and $334,564 (15*$22,304). Total cost savings for industry and FDA range between $651,891 ($428,848+$223,043) and $977,836 ($643,272+$334,564) (see table 2 below).

Table 2.-- Estimated Annual Benefit of the Proposed Rule

Estimated Number of Waivers	Industry			FDA Review (160 hours)	Total
	Scientist (80 hours)	Regulatory Affairs (240 hours)	Total		
10	$100,672	$328,176	$428,848	$223,043	$651,891
15	$151,008	$492,264	$643,272	$334,564	$977,836

Note: Totals may not add up due to rounding off. Average hourly wage rate is $125.84 for a scientist, $136.74 for a regulatory affairs manager, and $139.40 for an FDA FTE.

There could be additional benefits, which we cannot quantify or monetize, arising from cases where sponsors begin clinical studies—and thereby incur medical product development costs—without first consulting with FDA and later learn that clinical studies are not feasible.

D. Costs of the Proposed Rule

Because the proposed rule would continue our current policy regarding the application of fixed-combination requirements to co-packaged products, it would not impose any additional costs either on manufacturers of co-packaged products or the related products described above. However, applying for a waiver would result in costs associated with preparing the required documentation (by industry) and review (by FDA).

To estimate costs we use a similar method and some of the data used in the benefits section. Specifically, we continue to assume that there would be between 10 and 15 requests for waivers each year. Using time reporting data, we estimate that it could take approximately 25

hours for FDA to review waiver requests. To estimate the cost to industry we assume that it takes industry twice as many hours to prepare a request for waiver as it takes FDA to review, 50 hours. Furthermore, we assume that a regulatory affairs manager incurs 75 percent of the 50 hours (37.50 hours), and a scientist incurs 25 percent (12.50 hours) to prepare a waiver. Labor hours are valued using the same wage rates above: $139.40 for a fully-loaded FDA FTE, $136.74 for a regulatory affairs manager (Ref. 1), and $125.84 for a scientist (Ref. 1). FDA welcomes public comment on the accuracy of our assumptions regarding total sponsor preparation time, the allocation of hours across occupations, and the types of occupations included in the analysis.

Multiplying the labor cost by the estimated number of waivers, we estimate that the unit cost for industry to prepare one waiver is $6,701 (12.50*$125.84 + 37.50*$136.74) (rounded up). On the other hand, the cost of reviewing one such waiver for FDA is estimated at $3,485 (25*$139.40). Thus, the estimated annual costs of the proposed rule range between $101,858 and $152,787. This includes the estimated cost to industry of between $67,008 (10*$6,701)) and $100,511 (15*$6,701) and FDA review costs ranging between $34,850 (10*$3,485) and $52,276 (15*$3,485). Table 3 below summarizes our estimates.

Table 3.--Estimated Annual Costs of the Proposed Rule

	Industry				
Estimated Number of Waivers	Scientist (12.50 hours)	Regulatory Affairs (37.50 hours)	Total	FDA Review (25 hours)	Total
10	$15,730	$51,278	$67,008	$34,850	$101,858
15	$23,595	$76,916	$100,511	$52,276	$152,787

Note: Estimates may not add up due to rounding off. Average hourly wage rate is $125.84 for a scientist, $136.74 for a regulatory affairs manager, and $139.40 for an FDA FTE.

E. Summary of Benefits and Costs of the Proposed Rule

Table 3 below summarizes the estimated annual costs and benefits of the proposed rule. We estimated the benefits and costs associated with reduction in review time that could arise from clarifying the requirements for co-packaged and fixed-combination products. There could be other benefits, which we are unable to quantify or monetize, associated with unnecessary product development costs arising from the lack of specificity on the requirements for co-packaged drugs. Therefore, the estimated benefits of the proposed rule could be underestimated. Estimated annual benefits range between $651,891 and $977,836. Estimated annual costs range between $101,858 and $152,787. The estimated annual net benefits (benefits minus costs) range between $550,033 and $825,049 (see table 4 below).

Table 4.--Summary of Benefits and Costs of the Proposed Rule

Description	Low	High	Average
Benefits	$651,891	$977,836	$814,863
Costs	$101,858	$152,787	$127,322
Net Benefits	$550,033	$825,049	$687,541

F. Analysis of Regulatory Alternatives to the Proposed Rule

1. No Change in Regulation

FDA has been reviewing applications of co-packaged drugs on a case-by-case basis by applying the statutory standards for safety and effectiveness as well as other applicable regulations for new drugs. A simple alternative would be to leave the current regulation unchanged. This alternative would not impose additional costs to applicants or interested parties who request a waiver; however, our analysis above suggests that the costs associated with the

lack of regulation can result in costs greater than the cost of a waiver. Thus, under this alternative, any benefits from clarifying and harmonizing the requirements would not be realized.

2. Publish Additional Guidance

FDA has published a set of guidance documents that provides recommendations for some of the products covered under the proposed rule (see for example, Refs. 2 and 3). Because FDA's guidance documents do not establish legally enforceable responsibilities or requirements, without regulation, it is uncertain whether all applicants or interested parties will receive the information necessary when deciding whether to develop or market novel medical products.

II. Initial Regulatory Flexibility Analysis

FDA has examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. This analysis, together with other relevant sections of this document, serves as the initial regulatory flexibility analysis required by the Regulatory Flexibility Act.

The Small Business Administration (SBA) uses different definitions for a small entity for different industries. Using SBA size definitions for small entities, a firm categorized in NAICS code 325412 (Pharmaceutical Preparations) is considered small if it employs fewer than 750 employees (Ref. 4). Data on the types of applicants or interested parties that have submitted an application or submission for FDA review indicates that 50 percent of the firms covered by the

proposed rule would be considered small (see the first two columns of table 4 below).[4] We present the number for all establishments in NAICS code 325412 and for firms employing 0–9, 9–49, 50–99, 100-749 and 750+ employees. This breakdown allows us to investigate whether there would be any disproportionate effects among small-size firms.

Table 4.-- Estimated Impact of the Proposed Rule on Small Business Entities

Number of Employees	Number of Firms	Percent of Firms	Total Sales (in millions)	Average Sales (in millions)	Unit Cost as a Percent of Average Sales
0-749	38	50.0%	$150,883	$3,971	0.00017%
0-9	8	10.5%	$108,085	$13,511	0.00005%
10-49	6	7.9%	$27.0	$5.0	0.14842%
50-99	3	3.9%	$12,870	$4,290	0.00016%
100-749	22	28.9%	$11,607	$528	0.00127%
750+	38	50.0%	$3,524,277	$92,744	0.00001%
Total	76	100.0%	$3,675,161	$48,357	0.00001%

In section D, we estimated that the average unit cost of a waiver to a sponsor is $6,701. Using this estimate and matching the list of sponsors affected by the proposed rule to proprietary data from Dun & Bradstreet, Inc.--which includes sales and employment information--we determine the unit cost as a percent of the total sales for a typical firm in the pharmaceutical industry. We present our results in the last three columns of table 4. The average annual sales for entities that employ fewer than 750 workers are $3.97 billion and over $48.36 billion for entities with more than 750 employees. The unit cost of a waiver as a percent of the average of

[4] Using data at the establishment level implicitly assumes that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

value of sales for a typical firm would be small—less than 0.15 percent of average sales for firms with 10-49 workers and even smaller for other small-size firms. On the other hand, for a large size firm the unit cost as a percent of average sales is very small—approximately 0.00001 percent.

The analysis of the effect on small versus large entities indicates that the proposed rule would not impose any significant costs on manufacturers of fixed-combination or co-packaged drugs. Thus, we propose to certify that the rule would not have a significant economic effect on a substantial number of small entities, and seek comments or data on this analysis or conclusion.

III. References

1. U.S. Bureau of Labor Statistics. "May 2012 National Occupational Employment and Wage Estimates," May 2012 Occupational Employment Statistics, http://data.bls.gov/oes/, accessed August 19, 2013.

2. Food and Drug Administration, "Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination," June 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf, accessed August 19, 2013.

3. Food and Drug Administration, "Guidance for industry: Fixed Dose Combination, Co-packaged Drug Products, and Single-entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV," October 2006, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf, accessed August 19, 2013.

4. U.S. Small Business Administration. "Table of Small Business Size Standards Matched to North American Industry Classification System Codes," January 7, 2013, http://www.sba.gov/sites/default/files/files/Size_Standards_Table.pdf, accessed August 19, 2013.