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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph;
Docket No. : FDA–2015–N–1260

March 22, 2016

Dear Sir or Madam:

Bayer is pleased to submit these comments in response to the Food and Drug Administration's ("FDA's") Federal Register notice issued on December 23, 2015, requesting comments on the Proposed Rule entitled "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)[1]

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Bayer is a U.S.-based division of Bayer AG, one of the world's leading innovative companies in the healthcare and medical products industry. Bayer combines the activities of the Animal Health, Consumer Health, Medical Care, and Pharmaceuticals divisions. With more than 6,000 healthcare employees across the United States, Bayer aims to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases. We focus our efforts where we can have the most beneficial impact on the lives of those who depend on over 150 years of experience researching and developing new pharmaceuticals and medical devices.

General Comments

As a member of the Consumer Healthcare Products Association ("CHPA"), Bayer has reviewed the Proposed Rule with CHPA and is in agreement with the comments provided by organization.

Bayer supports the FDA's intent to harmonize the requirements for prescription and non-prescription fixed-dose combination and co-packaged drug products and make the rules consistent with long-standing FDA policy.

[1] Fed. Reg. Vol. 80 No. 246, pp. 79776-79795

Bayer is concerned, however, that the proposed definition of "co-packaged drug" is overly broad and could lead to consumer confusion. Bayer believes the definition of co-packaged should be modified to qualify "intended to be used together" to include "as evidenced by their labeling for use for the same indication in the same population". This would exclude products from the definition of "co-packaged drug" whose labeling does not treat the same symptoms in the same population. These are the products that FDA wishes to exclude from the proposed rule that are co-packaged and labeled as "value", "convenience" or other similar words. Based upon the revised definition, these products should no longer be labeled as "value", "convenience" or other similar words.

Bayer is concerned that use of "value" and "convenience" for co-packaged products solely because they are not intended to be used for the same indication in the same population could cause confusion for consumers; our proposed definition would eliminate the requirement to use those terms for this group of products. Consumers see and are familiar with a variety of product packaging that is currently on the market that has samples or other unrelated items attached. Regardless of whether labeled with "value", "convenience" or other similar words, it is clear from their labeling that the products are not intended or implied to be used together. In addition to existing familiarity, Bayer remains concerned about the unintended consequences related to the overuse of the terms "value" and "convenience" in the context of co-packaged products, which could be further complicated by a change in the meaning of the words over time. Bayer believes that putting a subjective term in the proposed rule would not serve the public interest.

Proposed 21 CFR §300.60 provides for a waiver from the requirements of §300.53 for a co-packaged drug that is the subject of a pending application or a combination of active ingredients under consideration for inclusion in an OTC monograph if certain conditions, as described in §300.60(a)(1) and (a)(2), are met. Bayer suggests that the FDA address timelines for the review of the waiver based upon the regulatory feasibility in guidance. In addition, Bayer believes that the guidance should include sufficient details to ensure that the waiver process does not become, by default, a review of the labeling of the proposed co-packaged products rather than an assessment of the regulatory feasibility of the proposed co-packaging.

Specific Comments

Specific Comments on Text		
Reference	**Comments**	**Proposed Change (if applicable)**
§300.50 (79794) Section III 4 (79781)	In proposed 21 CFR §300.50, the Agency defines co-packaged as follows: *Co-packaged drug* is a product that contains two or more separate drugs in their final dosage forms that are intended to be used together for a common or related therapeutic purpose and that are contained in a single package or unit.	Bayer believes that the Agency should modify the proposed definition to qualify "intended to be used together" by including the language "as evidenced by their labeling for use for the same indication in the same population". This would remove products from the definition of "co-packaged drug" whose labeling does not treat the same

	In the preamble, the Agency states that two products shrink-wrapped together would meet the definition of co-packaged drugs and further states that the act of shrink-wrapping two products together in the absence of any alternative explanation such as "convenience" or "value" would be an implied claim that the products are intended to be used together. The Agency proposes that," in the absence of another explanation, packaging two products together makes an implied claim that they are safe and effective when used together. Without proper approval, these products are considered unapproved drugs under 505(a) of the FD&C Act." The marketplace contains numerous examples of instances when co-packaged drug products are intended to be used together. Considering, for example, products intended for relief of symptoms of the common cold, there may be a variety of single ingredient products that may be co-packaged with the intention that they can be used simultaneously for symptoms of the common cold. These would be compliant with proposed §300.51 as long as they are described in §341.40. Likewise, one could propose instances where a manufacturer chooses to co-package products together without any intention of positioning the products for simultaneous use and without the desire to label the product as a "convenience" or "value" package. Examples may include: (i) Co-packaging of an adult product with a pediatric version of the same product. (ii) Co-packaging of a sunscreen (prevent sunburn) and external analgesic (treat the pain resulting from sunburn).	indications in the same population.
§300.51 and	Proposed 21 CFR §300.51 notes that the	Bayer suggests that the Agency

§300.53 (79794)	rule is applicable to "both prescription and OTC fixed-combination and co-packaged drugs …and to combinations of active ingredients under consideration for inclusion in an OTC monograph in accordance with part 330 of this chapter." Reference is further made to 21 CFR Part 341 (Cold, cough, allergy, bronchodilator and asthmatic drug products for over-the-counter human use) and, specifically, 21 CFR §341.40 (Permitted combinations of active ingredients). Bayer believes that 21 CFR §341.40 does not consider the potential for the co-packaging of the applicable cough/cold active ingredients but, rather, limits consideration to the fixed combinations of these actives in a single dosage form. Reference is made to a theoretical co-packaging (via shrink-wrapping together) of a menthol lozenge product and internal analgesic product. Menthol can be used as a topical (lozenge) antitussive under §341.14(b) (2) and §341.74(d) (2) (iii). As per the combination cough-cold monograph (§341.40(l)), any single oral antitussive may be combined with any analgesic-antipyretic active ingredient. This precludes the combination of a menthol lozenge with an analgesic-antipyretic active ingredient because menthol has to be in a topical dosage form. Proposed 21 CFR §300.51 effectively eliminates the possibility of this co-packaging because it is not considered under by 21 CFR §341.40(l). Proposed 21 CFR §300.53(a) notes the requirements that combinations of active ingredients under consideration for inclusion in an OTC monograph and fixed-combination and co-packaged drugs must meet. Specifically, each active ingredient makes a contribution to the effect of the	reconsider the overarching impact of proposed 21 CFR §300.51 and 21 CFR §300.53 in light of the apparent singular focus of 21 CFR §341.40 on fixed combinations of the cough/cold actives in a single dosage form. 21 CFR §341.40 does not consider the potential for co-packaging of products with these actives and therefore it is not appropriate to rely on this regulation as a basis for proposed 21 CFR §300.51. The example cited above by Bayer is just one of many potential similar examples which could be cited. In addition, this example only considers the cough/cold actives –OTC actives from other therapeutic categories may have similar examples that would be relevant. There is insufficient time for Bayer to construct a regulatory framework which would address the issue which we have raised. Bayer would be willing to further discuss this with the Agency as appropriate.

	combination (e.g., enhances safety or effectiveness of an active or minimizes the potential for abuse of an active) and the dosage of each active assures that the combination is safe and effective and provides rational concurrent therapy. Under proposed 300.53(c), a company wanting to shrink wrap (i.e., co-package) the example oral analgesic-antipyretic active ingredient (labeled for relief of minor aches and pains due to the common cold) and topical menthol lozenge (labeled for relief of cough due to a cold) could not do this without filing a new drug application or a submission under Part 330 to support the inclusion of a combination in an OTC monograph. Given that the products are both labeled to relieve symptoms of the common cold, the products could be used together. Thus, proposed §300.53 would prevent these products from being co-packaged (shrink wrapped) together without prior approval or a waiver from the Agency.	
Section IIB (79780)	Reference is made to the preamble (80 FR 79776 at 79780) statement: "Co-packaged day-night cough-cold products might, for example, be included in the monograph for OTC cough-cold drug products in §341.40 (21 CFR §341.40), and the monograph could specify the appropriate labeling for the co-packaged drug, if needed." Bayer is concerned that the example used in the preamble suggests that the monograph for OTC cough and cold drug products (21 CFR §341.40) should be modified to address the co-packaging of day-night cough and cold products. Reference is made to Part 341 (Cold, Cough, Allergy, Bronchodilator and Anti-asthmatic Drug Products) and Part 338 (Nighttime Sleep-Aid products). Neither	Bayer would like the example removed from the preamble in the final rule. Additionally, Bayer disagrees of the modification of 21 CFR §341.40 to include labeling for co-packaged day-night cough-cold products. .

	the labeling presented in §341.85 (combination cough and cold actives) nor the specific labeling of the cough and cold actives as provided in §341.72 (antihistamines), §341.74 (antitussives), §341.78 (expectorants), §341.80 (nasal decongestants) or as presented in the tentative final monograph for internal analgesics (53 FR 46204) limit an active ingredient to use only during the day or night. In contrast, the labeling in §338.50 contains labeling restrictions limiting the use of the product at bedtime. The labeling presented in §341.85, §341.72, §341.74, §341.78 and §341.80 provide information to the consumer for additional doses of the active; the labeling in §338.50 provides dosing information for an initial dose and does not provide information regarding subsequent doses. There is nothing in the labeling of day and night products that suggests or states that the products are to be used together simply because they are co-packaged together. Regardless of whether a product is intended for use during the day or night, the product has to have labeling for the safe and efficacious use of the product. Therefore, both the day and night component of the co-packaged product would require full labeling and would have to comply with the specific labeling requirements in 21 CFR Part 201 Subpart C –specifically those impacting the statement of identity and the net quantity of contents statement. A review of the co-packaged day and night products from the category leaders found that all products reviewed also listed the specific symptoms for which each product is used. In many cases the day and night products co-packaged together were further differentiated by the use of color, other graphical elements and by identifying the	

	“night” product as “nighttime” or “night”.	

We thank you for your consideration of these comments. If you have any questions, please do not hesitate to contact me by phone at 862.404.4036 or via e-mail at todd.paporello@bayer.com.

Sincerely,

Todd Paporello

Digitally signed by Todd Paporello
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