



11 February 2013

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

Subject: [Docket No. FDA–2012–D–1005] Draft Guidance for Industry on Safety Considerations for Product Design to Minimize Medication Errors

Dear Sir/Madam,

ISPE welcomes the opportunity to comment on the “Draft Guidance for Industry on Safety Considerations for Product Design to Minimize Medication Errors”.

We believe it would be beneficial to revise the Draft Guidance to specifically recommend that drug developers consider the use of adherence packaging in early stages of drug product design.

According to the Federal Register notice announcing the Draft Guidance, a “second guidance will focus on minimizing risks with the design of drug product container labels, carton labeling, and packaging configurations.”<sup>1</sup> Although the present Draft Guidance touches on such issues, we believe it is appropriate to comment now on the benefits of adherence packaging and labeling. We agree, as noted in the Draft Guidance, that “labeling [and] packaging . . . have been identified as key system elements that have great influence on medication use, [and] any weaknesses or failure in the design of these elements can cause medication errors that lead to patient harm.”<sup>2</sup> We also agree that these are factors that should be considered at the early stages of drug development. Moreover, we agree with the statement in the Draft Guidance that “factors influencing the choice of a container closure system for commercial distribution of the finished product should go beyond stability or ease of manufacturing,” but also “should protect against improper use.”<sup>3</sup>

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<sup>1</sup> 77 Fed. Reg. 74,196-97 (Dec. 13, 2012).

<sup>2</sup> See Draft Guidance at 4.

<sup>3</sup> See *id.* at 11.

The Draft Guidance references the 2006 Institute of Medicine (IOM) report on *Preventing Medication Errors* throughout. That report highlights the benefits of unit-of-use packaging, and blister packs and calendar blister packs in particular. The well-established benefits of such packaging, as documented in the IOM report and references cited within, include the following:

- Promotion of child safety by providing greater protection against accidental poisoning;
- Prevention or minimization of errors resulting from repackaging at the pharmacy;
- Tamper evidence; and
- (Most significantly for purposes of these comments) improving adherence to treatment regimens due to being easier for consumers to use.<sup>4</sup>

With respect to the last point above, the IOM report found:

The strategy of using calendar blister packs could help large numbers of patients (including seniors, children, and those challenged by cognitive, physical, or functional impairment) take their medication more reliably and safely and enhance their treatment outcomes.<sup>5</sup>

Since the publication of the IOM report, at least two additional key studies documenting the benefits of adherence packaging have been published. In one study, adherence and persistence were compared in 9,266 matched patients (4,633 in each cohort) taking antihypertensive drugs.<sup>6</sup> One cohort received their drugs in calendar blister packs (30-day), and the other did not. The cohort that received calendar blister packs had significantly better adherence as measured by increases in medication possession ratio and proportion of days covered; it also had significantly better persistence as measured by shorter gaps between refills over an 11-month period.

Another study examined pharmacy dispensing data before and after a switch of lisinopril packaging from vials to exclusively calendar blister packs.<sup>7</sup> A control group consisted of those who filled prescriptions for enalapril, which was not offered in calendar blister packs. The sample size consisted of 76,321 new users and 249,040 prevalent users. Use of calendar blister packs was associated with significantly greater adherence, as measured by proportion of days covered; and significantly greater persistence, as measured by length of therapy.

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<sup>4</sup> See IOM Report at 283.

<sup>5</sup> *Id.* at 284.

<sup>6</sup> Dupclay, L. *et al.* (2012) "Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence," *Patient Preference and Adherence* 6, 499-507.

<sup>7</sup> Zedler, B.K. *et al.* (2011), "A Pharmacoepidemiologic Analysis of the Impact of Calendar Packaging on Adherence to Self-Administered Medications for Long-Term Use," *Clinical Therapeutics* 33:5, 577-593.



In light of the IOM report and the studies briefly summarized above, as well as the vast amount of additional supportive data cited within these references, **we submit that it would be appropriate to make a stronger and more affirmative recommendation in the final version of the Guidance for manufacturers to consider the use of adherence packaging, and calendar blister packs in particular, during early stages of drug product design to help minimize medication errors.**

In addition, please find comments related to specific wording in the document attached and following this letter. Thank you again for the opportunity to provide these comments.

Yours sincerely,

President/CEO, ISPE



Attachment 1

	Line Number	CURRENT WORDING	PROPOSED CHANGE	RATIONALE
1.	127	Therefore, the goal is to design a drug product that enables safe and correct use and minimizes the chance for health care practitioners, patients, and caregivers to make mistakes.	Revise and add highlighted text: Similarly, sufficient data exists to support the use of certain labeling and packaging features that have been proven to improve patient medication adherence and persistence, such as child-resistant calendar blister packaging. Therefore, the goal is to design a drug product that enables and facilitates safe and correct use and minimizes the chance for health care practitioners, patients, and caregivers to make mistakes.	Provides additional clarity.
2.	334 - 340	During development of an extended- or delayed-release product it is helpful to make the strengths of the extended- or delayed-release product distinct from the immediate release products. Failures in prescribing, such as omission of modifiers or incorrect use of suffixes, can lead to dispensing and administration of the immediate-release product instead of the intended extended- or delayed-release product. This can occur because all product characteristics overlap, or the strength is achievable from the marketed immediate-release product strength.	Insert the following paragraph at line 341: Sponsors should make selections of container closure systems and associated labeling attributes that not only accommodate product stability and manufacturing needs, but that protect against improper use. Manufacturers should consider the use of appropriately evaluated child resistant adherence packaging, and calendar blister packs in particular, during early stages of drug product design (specifically phase II/III) to help minimize medication errors.	The same level of design controls should not be applied to dosage forms used in very early clinical studies. While it is important for the drug developer to consider the items addressed in the guidance, even at the earliest stages, it may not necessarily be realistic or even necessary to implement these controls. Phase 1 studies are generally conducted in very well controlled environments. As such the possibility of errors is minimized, though clearly not entirely prevented. It may add unnecessary burden and cost to require implementation of such design elements.