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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Docket No. FDA-2011-D-0074: Draft Guidance for Industry on Medication Guides—
Distribution Requirements and Inclusion of Medication Guides in Risk Evaluation and
Mitigation Strategies**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's "Draft Guidance for Industry on Medication Guides—Distribution Requirements and Inclusion of Medication Guides in Risk Evaluation and Mitigation Strategies (REMS)." In general, BIO welcomes the approaches that FDA has taken regarding approval of a Medication Guide (MedGuide) outside of a REMS framework, and our comments below are intended to provide further clarity for Sponsors, health care providers (HCPs), and patients.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

BIO commends the FDA for taking this step to distinguish MedGuides approved under the Part 208 regulations from MedGuides required subject to a REMS. It is important to note that most approved REMS consist of only communication-based risk management strategies, rather than the more restrictive Elements to Assure Safe Use (ETASU). The previous practice of including all MedGuides

under a REMS placed significant workload demands on FDA and industry without clear added value. The Draft Guidance acknowledges there would be considerable efficiencies if MedGuides were implemented outside of the REMS framework. This change has the dual benefit of enhancing benefit/risk communication towards patients while reserving full-scale REMS implementation for elements to ETASU programs, so that all stakeholders in the healthcare delivery system can focus more resources on the most critical risk minimization activities.

As part of the FDA's Patient Medication Information (PMI) Initiative, BIO and FDA have also stated the shared goal of having one unified form of patient information to avoid redundancy and public confusion around the distribution of MedGuides, patient package inserts, and Consumer Medication Information (CMI). BIO supports FDA's ongoing efforts to move to a single patient oriented leaflet that presents balanced benefit and risk information, which would incorporate the relevant safety information now contained within MedGuides and further promote patients' ability to make an informed decision about their health.

BIO requests the following clarifications in support of the Draft Guidance.

A. Distribution of MedGuides in Certain Settings:

1. What Constitutes a "Material Change"?

The Draft Guidance states that a MedGuide must be distributed in four situations, including "The first time a drug is dispensed in an outpatient setting of any kind, after a Medication Guide is materially changed. FDA plans to specify in the letter approving a revised Medication Guide when a change is considered to be a material change and applicants will be directed to notify healthcare professionals that a material change was made." (lines 197-200)

The distribution requirement is contingent upon a "material change", but the Draft Guidance does not address what would constitute a material change. The criteria that define a material change should be described in the Final Guidance and should be transparent to Sponsors, healthcare providers (HCPs) and patients.

At a minimum, we suggest that the Final Guidance should explicitly state that minor corrections such as typographical errors or grammatical changes would not be considered material changes to a MedGuide.

2. How will Pharmacies and HCPs be notified of a "Material Change"?

Furthermore, it is unclear how pharmacists and HCPs will be notified of a material change and subsequent requirement to distribute a MedGuide. While the recommendation to distribute revised MedGuides is reasonable, it may be a challenge to operationalize if the pharmacy does not know when a MedGuide was materially changed in relation to the last outpatient dispensing event. We request that FDA further clarify the method of notification, such a Dear Health Care Provider (DHCP) letter, for notifying HCPs of a change and their responsibilities to dispense the MedGuide.

To help manage the process for distributing MedGuides that have been materially changed, FDA may also consider adding a box at the top of MedGuides similar to the prescription product labeling that indicates the date of first approval, date of last material revision, and the section that was changed.

3. Please Clarify the Phrase “The First Time”

It is also unclear whether the Draft Guidance is recommending that a MedGuide be provided the “first time” the drug is dispensed to a particular healthcare professional or the first time for a particular patient. It would be preferable to stipulate ‘by patient’ and this would help to ensure that the HCP remembers to discuss the information in the MedGuide with the patient. Please consider changing the sentence structure to clarify the intent. BIO has provided a number of line-by-line edits to clarify our understanding of the intent:

- **Line 195-196:** ~~The first time a~~ When a drug is dispensed to a particular healthcare professional for administration to a patient for the first time in an outpatient setting, such as in a clinic or dialysis or infusion center.
- **Line 197-200:** ~~The first time~~ When a drug is dispensed in an outpatient setting of any kind, to a particular patient the first time after a Medication Guide is materially changed. FDA plans to specify in the letter approving a revised Medication Guide when a change is considered to be a material change and applicants will be directed to notify healthcare professionals that a material change was made.
- **Line 202-206:** We believe the Medication Guide should be dispensed in outpatient settings, even when the drug is dispensed to a healthcare professional for administration to the patient, the first time the drug is dispensed for that patient, and if the Medication Guide is materially changed. In these instances, we would expect the Medication Guide to assist the healthcare professional in communicating important information about the drug to the patient.
- **Line 212: Table 1, Row 1, Column 3:** Medication Guide Distributed At Time of First Dispensing to a Particular Patient
- **Line 212: Table 1, Row 1, Column 4:** Medication Guide Distributed to a Particular Patient the First Time After a Medication Guide Materially Changed

4. MedGuides should be Complementary to Health Care Providers Discussions with Patients:

We note that there is little value in approving, producing, and distributing these materials if patients and healthcare providers do not read them to better understand a given product’s benefits and risks. The Draft Guidance states that “In these settings, the drug will be dispensed to a patient by a healthcare professional who should provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or followup that may be required as appropriate, and answer any questions the patient may have.” (lines 179-182) While we agree that HCPs *should* provide the patient instructions on appropriate drug use and side effects, this patient-HCP dialogue does not always occur and manufacturers have minimal control over how well HCPs perform this task. We remain concerned that going forward, FDA may place a greater emphasis on Sponsors assessing whether and how well HCPs are communicating key risk information, without adequate recognition that industry has little control regarding patient receipt of a MedGuide. Therefore, we request clarification as to whether and how the FDA intends to exercise enforcement and to whom the enforcement would be directed.

In addition, we suggest that FDA describe the educational efforts to be undertaken to ensure that the healthcare community understands their role in distribution of MedGuides under this Guidance. We request that FDA assume a leadership role in coordinating these educational initiatives with stakeholders. The better educated the healthcare community is on their responsibilities with regard to distribution of MedGuides, the greater the likelihood that this important information will be appropriately provided to patients as required.

B. MedGuides as Part of REMS:

1. A Clear Process and Timely Process for Notifying the Sponsor of a REMS MedGuide Requirement

Under the Draft Guidance, FDA retains the discretion to require a MedGuide either outside of REMS under Part 208 or as part of REMS. The Guidance states that “In other cases, FDA may determine that a Medication Guide and other elements of a REMS are necessary to ensure that the benefits of a drug outweigh the risks, such as elements to assure safe use. In most cases, FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. However, FDA will include a Medication Guide in a REMS that does not include elements to ensure safe use if we determine that having the Medication Guide without a REMS will not be sufficient to ensure that the benefits of the drug outweigh the risks.” (lines 230-236)

The Draft Guidance does not indicate when, or how, a Sponsor will be informed of the requirement for a new MedGuide and whether it will be part of a REMS. We ask that FDA clarify when/how that communication with the Sponsor will take place, especially during the NDA/BLA review period. Regarding timing, BIO has consistently urged FDA to initiate risk management and benefit/risk communication discussions as early as possible in the review cycle. Regarding the process FDA will use to communicate whether a new MedGuide is needed and will be part of a REMS, we note that FDA may need to establish a new process separate from the existing processes for issuing a REMS notification letter, and for sending initial labeling comments to industry (by the target date in the 74-day letter). If FDA does not establish a new process with associated clarity around timing, industry could believe that a MedGuide is not needed, or is not part of a REMS, simply because the Sponsor did not receive a REMS notification letter. If the Sponsor receives notification late in the review cycle that a MedGuide is needed, perhaps as part of a REMS, this could result in a major amendment/extension or another review cycle. We request clarification of whether FDA will exercise enforcement discretion in such cases.

2. Procedure for Requesting Removal of MedGuides from REMS

The Draft Guidance also discusses the process for how a Sponsor can propose to have a MedGuide removed from a REMS through submission of a prior approval supplement. “Applicants with a REMS that includes a Medication Guide, a communication plan, and a timetable for assessment also may submit a prior approval supplement that proposes a REMS modification to remove the Medication Guide from the REMS, if they do not believe that a Medication Guide that is a part of the REMS is necessary to ensure that the benefits of the drug outweigh the risks.” (lines 241-246)

We request that FDA provide further guidance regarding situations where it would be justifiable or what justification would be required to propose elimination of a REMS. We also suggest that FDA provide more details regarding the contents of this prior approval supplement for MedGuide-only

REMS. In particular, how would the content of the supplement differ for a MedGuide-only REMS versus a request to remove a MedGuide from a REMS that also has a Communication Plan?

3. Communication Plan REMS

While the Sponsor can propose that a MedGuide be removed from a REMS, the Draft Guidance does not address whether Sponsors may also request that the Communication Plan be removed from the REMS, thus, in some cases, eliminating the REMS entirely. We request clarification on this option because we understand that FDA has suggested this approach for some products. This would be particularly relevant if the MedGuide and Communication Plan share similar goals.

In addition, it would be helpful if FDA could provide examples of what situations (and rationale) would warrant keeping the Communication Plan and timetable for assessments in place when requesting removal of the MedGuide from a REMS with MedGuide and Communication Plan elements.

4. Impact on REMS Assessments

Although it is implicit in the Draft Guidance, we request that the document clearly state that the removal of the REMS eliminates the need to perform an assessment of patient understanding of the risks, irrespective of the source. Additionally, we request more information regarding the impact that removal of a MedGuide has on REMS goals overall and future assessments of REMS that still contain Communication Plans. We suggest that this might be handled by the Sponsor removing any MedGuide-related goals and information on distribution and assessment of the MedGuide and retaining Communication Plan-related goals and activities.

CONCLUSION:

BIO appreciates this opportunity to comment on FDA's "Draft Guidance for Industry on Medication Guides—Distribution Requirements and Inclusion of Medication Guides in Risk Evaluation and Mitigation Strategies." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

<u>LINE</u>	<u>SECTION</u>	<u>PROPOSED CHANGE</u>
II. DISCUSSION		
<i>A. Distribution of Medication Guides in Certain Settings</i>		
Lines 179-182:	“In these settings, the drug will be dispensed to a patient by a healthcare professional who should provide the patient instructions...”	We believe that Line 179 contains an error. It should read, "In these settings, the drug will be administered dispensed to the patient by a healthcare professional who should....."
Lines 213-218:	“Please note that when a drug is subject to a REMS that includes specific requirements for the review of a Medication Guide (possibly in conjunction with distribution), FDA does not intend to exercise enforcement discretion regarding those specific requirements set forth in the REMS (e.g., when healthcare providers are required to review the Medication Guide with patients before patients are enrolled in a REMS program as an element to assure safe use).”	This is a little unclear as stated and would be better to indicate that MedGuide discussions are still required. However, if that is not possible due to the statutory language, we suggest bolding the following lines for emphasis: Please note that when a drug is subject to a REMS that includes specific requirements for the review of a Medication Guide (possibly in conjunction with distribution), FDA does not intend to exercise enforcement discretion regarding those specific requirements set forth in the REMS (e.g., when healthcare providers are required to review the Medication Guide with patients before patients are enrolled in a REMS program as an element to assure safe use).