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May 8, 2012

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

Re: Docket No. FDA–2005-D-0339: Draft Guidance on Drug Safety Information—FDA's Communication to the Public

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance on Drug Safety Information—FDA's Communication to the Public."

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:

A. Safety Information should be Communicated in the Balanced Context of Benefit/Risk, Health Outcomes, and Scientific Uncertainty:

BIO believes that the Draft Guidance makes some important clarifications in FDA's risk communication policies that will benefit the public health. For example, the Draft Guidance states that a Drug Safety Communication (DSC) generally communicates the following information (lines 272-276):

- A summary of the safety issue and the nature of the risk being communicated
- The established benefit or benefits of the drug being discussed
- Recommended actions for health care professionals and patients, when appropriate
- A summary of the data reviewed or being reviewed by FDA

Since all drugs carry both benefits and risks which must be carefully evaluated by patients and their physicians, we support FDA's recognition that new safety information must be communicated in the context of the drugs intended use and benefit. As stated in the Draft Guidance, "FDA recognizes the potential public health implications of providing emerging drug safety information, and we are particularly concerned about possible unintended consequences, such as inappropriate modification or discontinuation of useful treatment." (lines 155-157) BIO fully agrees with this statement so that patients in consultation with their doctor have the full context of a drug's benefits and risks when making important decisions about their health. The public health is not necessarily advanced by communication of drug risks in the absence of a discussion of known benefits or the context of other commonly accepted risks.

BIO also supports the conclusion that FDA communications should be outcomes focused with clear advice for patients and healthcare providers on how to manage a risk, rather than just focusing on dissemination of facts or conclusions.

We appreciate the communication will also include a summary of the data reviewed or being reviewed by FDA. BIO recognizes the dual, and occasionally competing, goals of timely and relevant communication with the public and the need to ensure that the scientific findings are verified and accurate. However, we note that publication of analyses that have not been verified by quality systems to ensure accuracy of conclusions can lead to greater patient confusion in the long term. Uncertainty in a known or emerging risk is not well described in the guidance as a factor in when to communicate a safety issue to the public or in how the issue is assessed. We request that FDA please describe how the communication might differ based on the level of certainty about a specific risk. In addition to a summary of the data source, we encourage FDA to communicate the level of uncertainty associated with the safety signal and the type of evidence used to support the claim.

B. Communication with the Sponsor Prior to a Risk Communication

Adequate communication among FDA, regulated industry, and the public is a critical component of an FDA public health intervention. The Draft Guidance states that "FDA strives to notify the relevant Sponsor at least 24 hours before the first public communication that emerging safety information about its drug will be posted on the FDA Web site." (lines 478-480) In the event of a safety issue or enforcement action, we recommend that FDA notify the company involved earlier than 24 hours prior to any external FDA communication so that the company may develop complementary communications to the public and healthcare providers, or work collaboratively with FDA to establish a joint communication plan. We suggest FDA engage with Sponsors at least 48-72 hours in advance of communicating emerging safety information or results of manufacturing site inspections (Form 483) which have implications for patient safety, to

the public. Companies need to prepare to respond to inquiries from media, international health authorities, advocacy groups, and consumers that will be triggered by FDA public announcements.

For example, although MAPP 6700.4 states the Office of New Drugs (OND) safety regulatory project manager will notify the Sponsor once a DARRTS Tracked Safety Issue (TSI) has been created, it does not state that FDA will communicate to the Sponsor regarding FDA web posting of alerts or communication on this topic. In addition, MAPP 4151.6 on the Drug Safety Newsletter states that Sponsors of products discussed in the newsletter will be notified by fax only 24 hours before posting of the newsletter.

There is need for more communication and coordination between FDA and Sponsors to minimize the potential for conflicting information and provide multiple channels of communication to better inform patients and physicians.

C. Communicating when a Safety Issue is Resolved

The guidance does not outline when and how FDA will communicate a decision that a potential safety issue is no longer deemed "potential" or an issue altogether. We request the addition of details regarding such communication.

Additionally, the guidance does not outline how it determines when to remove safety-motivated restrictions (for example, no longer requiring restricted distribution as part of a REMS program) and how that decision is communicated. We suggest that this information be added to the guidance.

Section 11 also addresses how drug safety information is updated and archived. It is helpful that FDA plans to identify updated information in DSC's with the month and year in which it was identified. Creating a permanent archive (still publicly available on the Web) for all DSCs, however, will create a situation where very old and stale safety communications, that have since been resolved, may be inadvertently accessed as a "live" issue. More fundamentally, permanently retaining old safety communications is at odds with the primary purpose for DSC's – informing patients and HCP's about *emerging* drug safety information. Once the issue has been resolved, the DSC is no longer a "timely communication" (line 52) – it is outdated. For important drug safety information, patients and HCPs should use the approved product labelling as their resource. Retaining closed out DSCs in a permanent archive that is still publicly accessible runs a real risk of misleading the public and creating an information overload, such that the important safety information – that which is found in the product's labelling – can become obscured.

While an issue is still under study, such as when clinical trials are still ongoing (lines 451-452) or evaluation of a complex issue is still underway (lines 450-451), then it may be appropriate to keep an archive of all DSCs involved with that particular issue. Once an issue has been resolved or the label has been amended appropriately, however, such as when FDA finds "sufficient evidence that a drug is not associated with a safety concern previously described by FDA as an *emerging* drug safety issue" (lines 439-440, emphasis

added), then the entire DSC thread for that issue should be removed from the DSC page, as it is no longer a "timely" communication of an "emerging" safety issue. Similarly, it is unclear what independent utility closed out DSC's would have for the public absent any regulatory action (line 445). Rather than a catch-all catalogue of information (which, by its very nature, could be incomplete or not substantiated), FDA should ensure that the DSC page remains focused on its stated purpose – providing timely information on emerging safety issues – and leave other regulatory vehicles, such as the product labelling or www.clinicaltrials.gov for ongoing trials – to serve their purposes. In 5, 10, 15 years time, the permanently archived reports will not provide any benefit to HCPs or patients due to their outdated nature and will only serve to be at most, distracting, and at worst, misleading, about a product's safety information.

FDA should revise Section 11 to reflect a "close-out" process for when a Drug Safety Communication has been effectively addressed and resolved, such that it no longer will reside in the Drug Safety Communications archive. In the Final Guidance, FDA should remove the sentence "*Updated DSC's, like all DSC's, are permanently archived on the Web site,*" (Lines 442-443) and replace it with a policy that will more accurately track to the purpose of DSC's and provide meaningful, as opposed to potentially misleading, incorrect information to patients and HCP's. It may also serve as a resource to document the strengths and limitations of the signal evaluation process. What was the result of all this risk communication? Was public health served?

D. Definitions of "Risk" and "Regulatory Action"

FDA should define what is meant by risk. In general, it seems to mean an adverse event or serious adverse event or medication error, but elsewhere it seems to imply other things, such as off-label use. We note that risk and signal evaluation are not necessarily interchangeable.

In addition, throughout the document, the term "*regulatory action*" is used, but not defined. For example, the Draft Guidance states that *"In recent years, FDA has begun making information on potential drug risks available to the public earlier — often while the Agency is still evaluating the data and determining whether any* ***regulatory action*** *is warranted."* For the sake of clarity, please provide examples of "regulatory action". FDA can take a number of regulatory actions in response to new safety information, including label changes, Risk Evaluation and Mitigation Strategies (REMS), market withdrawal, recalls, etc.

E. Addressing Sentinel Findings

We request that FDA clearly state and/or recognize that results from the FDA Sentinel Network should follow the processes outlined in both Draft Guidances before communicating Sentinel findings to the public. The FDA Sentinel Initiative falls under the active surveillance evaluations, which is mentioned in both guidances as a source of new, more serious adverse drug reactions.

F. Communicating Other Safety Issues

If off-label use, non-adherence, loss of efficacy, and counterfeit medications are important safety issues, these should also be included in "What this guidance is about," along with a description of how these issues would be communicated.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance on Drug Safety Information—FDA's Communication to the Public." Specific, detailed comments are included in the following chart. 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

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Lines 44-45	The term "*general*" seems vague; suggest using "*known/potential.*"	Suggest the following minor revision: "The ~~general~~ known/potential risks and benefits of a drug therapy are described in the product's prescribing information."
Lines: 49-51	The guidance states, "In recent years, FDA has begun making information on potential drug risks available to the public earlier — often while the Agency is still evaluating the data and determining whether any regulatory action is warranted." In reality, FDA often posts information online when it is initiating a tracked safety issue (TSI), at the start of the evaluation. The current statement implies that FDA only makes information public when the evaluation is further along.	Please change the statement to "In recent years, FDA has begun making information on potential drug risks available to the public earlier — often when a safety issue has just been identified or while the Agency is still evaluating the data and determining whether any regulatory action, such as label changes, Risk Evaluation and Mitigation Strategies (REMS), market withdrawal, recalls, etc. is warranted."
III. QUESTIONS AND ANSWERS		
2. How Does FDA Evaluate Drug Safety Information?		
Lines: 98-101 117-120	Both of these sentences use the term "surveillance evaluations."	At first mention, please explain the meaning of the term "surveillance evaluations," perhaps in the context of the Sentinel System.
Lines 110-113	*"Often, however, there is a period **of uncertainty while** FDA evaluates the emerging safety information to determine whether there is an important drug safety issue related…"* Please delete the word "uncertainty" as it suggests lack of expertise in evaluating data,	Please revise to the following: Often, however, there is an evaluation period ~~of uncertainty while~~ where there may not be sufficient evidence (information) to confirm or refute the emerging safety issue to determine whether…" Additionally, please incorporate language addressing how FDA will

	while the real issue is that there is insufficient data to allow the Agency to make a more definitive decision.	deal with missing information. For example, a situation where FDA or the Sponsor can neither confirm nor refute the safety issue, because the period of uncertainty is indefinite.
Line 124	*"Interpreting postmarket safety data **is complex**…"* Interpretation of postmarketing data is complex because it involves reports from patients and physicians who are using the drug in the real world setting, not in the controlled clinical trial setting. Thus these data are sometimes harder to interpret as opposed to data from clinical trials.	"Interpreting postmarket safety data submitted by patients actually using the drug or by physicians once the drug has been approved ~~is~~ can be complex. Postmarket safety analysis can include review of clinical data…"
Lines 130-132	Engagement with the Sponsor also appropriate to mention in this section.	Suggest including "**with the drug Sponsor**" if FDA intends to engage Sponsor in these discussions re: emerging safety issues. "We engage in robust and comprehensive discussions within the Agency and with the drug Sponsor regarding potential drug safety issues to ensure that all ~~points of view~~ relevant data are considered before making a decision on how to proceed."
Lines 140-142	*"As the Agency evaluates a drug safety issue to determine whether regulatory action is warranted, we may decide to communicate further information to the public at **appropriate points** during the decision-making process."* It is unclear what "***appropriate points***" during the decision making process would be.	We request that the FDA provide more information regarding what the "***appropriate points***" would be.
3. When Does FDA Communicate Emerging Drug Safety Information to the Public?		
Lines: 158-159	The guidance discusses "describing the nature of a safety concern and what is known about its relationship to a particular drug" in FDA's risk	Please acknowledge in the guidance that FDA sometimes relies on what is known about similar drugs, rather than a particular drug, to make decisions.

	communications. However, FDA sometimes takes action based on knowledge of drugs with a similar mechanism of action or disease target, rather than knowledge of a particular drug.	
Lines 165-168	*"Despite this tension, we lean toward early communication of emerging drug safety information unless, in our judgment, the information available is not reliable enough to be useful and could mislead the public. We recognize this means that, in some cases, we will have to say that a safety concern "has not yet been substantiated.""* We request that FDA provide clarity regarding the previous two sentences as we do not necessarily view the two sentences as conflicting. The first sentence implies that FDA would not release information that is unreliable versus the second statement states that FDA would issue it with a caveat "*has not yet been substantiated.*" We suggest deleting the word "**substantiated"** as the issue in most cases will be that there is a lack of, or insufficient, evidence to come to a definitive conclusion.	Please revise to the following: "We recognize this means that, in some cases, we will have to say that ~~a safety concern "has not yet been substantiated."~~ there is insufficient evidence to suggest that a definitive new safety concern has been identified." We also request FDA provide examples of what is "***not reliable enough***" to use.
Lines 174-175	*"FDA considers many factors in the course of evaluating an emerging drug safety issue and deciding whether emerging drug safety information should be made available to the public."* The list of factors in evaluating emerging drug	Please clarify if there are geographic considerations when considering factors (*i.e.*, how broadly drug is used globally?).

	safety issue does not address regional considerations.	
Lines 189-192	Lines 189-192 from the Draft Guidance would be useful to include within the actual Drug Safety Communication for clarity to the public.	We suggest including the following statement from the Draft Guidance in public communications for clarity to avoid "*possible unintended consequences*" (line 156). ***"The decision to provide information about an emerging drug safety issue does not necessarily mean that FDA has concluded there is a causal relationship between the drug and the adverse event described. Nor does communicating emerging drug safety information necessarily mean that FDA is advising health care professionals to limit their prescribing of the drug at issue."***
4. How Does FDA Communicate Important Drug Safety Information to the Public?		
Lines 206-208 & 227-229	*"FDA-approved prescribing information for health care professionals — and patient package inserts and Medication Guides for patients — is the primary source of established information about a drug's safety and efficacy…"* Lines 206-208 state that all drug safety communications include benefits along with its risk; however, "Medication Guide" is primarily a document to communicate risks to patients. "With all drug safety communications, FDA now makes a concerted effort to communicate the benefits of a drug along with its risk."	We request an update as to whether FDA plans to update the Medication Guide guidance such that benefit information can be included?
Lines: 214-217	The guidance describes FDA's cooperation with various groups to facilitate communication of drug safety issues to the public.	Please include manufacturers in the list of groups FDA works with to communicate safety issues to the public.

	Manufacturers are not mentioned, even though they often play an important role in communicating safety issues. The guidance should address the significant and important roles/responsibilities of the manufacturer in communicating safety information -- Either include this information in this section or put it into subsequent Section 9 "What Other Methods Are Used to Communicate Drug Safety Information?"	
5. What is FDA-Approved Labeling?		
Lines 227-229	"FDA-approved prescribing information for health care professionals — and patient package inserts and Medication Guides for patients — is the primary source of established information about a drug's safety and efficacy;"	See comment for lines 206-208 above.
6. What is a CDER Drug Safety Communications (DSC)?		
Lines: 268-302	This section of the guidance discusses Drug Safety Communications (DSCs). It is unclear what the Sponsor's role is in development of a DSC. When a safety issue is initiated, the Sponsor should at a minimum be informed and ideally consulted when preliminary results are available.	Add greater specificity regarding the Sponsor's role in development of and response to a DSC. We also ask if CDER will establish a call center to field questions regarding its safety communications?
Lines 287-288 & 294-302	*"To improve the clarity of our communications, FDA began using a single communication vehicle — the Drug Safety Communication — in early 2010."* *"During the evaluation period, FDA may issue a follow-up DSC as a public reminder, even if*	How does FDA avoid misinterpretation of the DSC as crisis communication tool? Consider use of standard text as suggested in comment regarding Section 3; Page 6, i.e., Lines 189-192. We request the FDA describe what would trigger a follow-up DSC

	no additional information is available since the original DSC was issued. Note: Although a DSC communicates important safety issues about marketed drugs, it is ***not*** *a crisis communication document."* In reference to the lines above, how does the FDA avoid misinterpretation of the DSC as crisis communication tool?	during the evaluation period.
9. What Other Methods Are Used to Communicate Drug Safety Information?		
Lines 365-375	*"Drug Sponsors also use various methods to communicate drug safety information. For example, a Sponsor might distribute a Dear Health Care Provider Letter (sometimes referred to as a Dear Doctor letter) to convey important information about a marketed drug. A Sponsor can issue a Dear Health Care Provider Letter on its own initiative or following a request or requirement by FDA. A Sponsor can be required to issue a Dear Health Care Provider Letter or other communication that is approved as part of a communication plan of a REMS. Dear Health Care Provider letters can be used to disseminate information regarding a significant hazard to health, to announce important changes in prescribing information, or to emphasize corrections to prescription drug advertising or prescribing information. Depending on the issue and whether the communication is tied to a regulatory action, FDA may notify the public when Sponsors issue a Dear Health Care Provider Letter."*	Given FDA's intention to use a single communication vehicle (Drug Safety Communication) for safety issues, what is the utility of a safety-oriented, non-REMS DHCP letter? What would be the circumstance that the DSC may be used instead of a safety-oriented non-REMS DHCP letter?

11. How Is Drug Safety Information Updated?		
Lines: 424-460	This section of the guidance describes how drug safety information is updated. How will FDA communicate matters that are no longer considered safety issues?	Explain how FDA will communicate that a specific matter is no longer considered a safety issue.
Lines 439-443	*"If data become available that provide sufficient evidence that a drug is not associated with the safety concern previously described by FDA as an emerging drug safety issue, FDA intends to update the information accordingly. In these instances, we plan to issue a new update of comparable prominence to the DSC to reflect this new information. Updated DSCs, like all DSCs, are permanently archived on the Web site."* This statement, which clarifies that FDA will take measures to retract/update any information previously communicated by FDA incorrectly regarding emerging drug safety information should be made more prominent and placed in section 3.	Please consider relocating the following statement in the guidance to section 3 for prominence. "If data become available that provide sufficient evidence that a drug is not associated with the safety concern previously described by FDA as an emerging drug safety issue, FDA intends to update the information accordingly."
13. Does FDA Involve Sponsors Before Making Emerging Drug Safety Information Public?		
Lines 476-480	*"FDA may solicit Sponsor input when appropriate, for example, to confirm the accuracy of factual information. FDA strives to notify the relevant Sponsor at least 24 hours before the first public communication that emerging safety information about its drug will be posted on the FDA Web site."* Is 24 hours notice sufficient for Sponsor notice (and even then, FDA states that it will "strive"	Please see our general comments which suggest that FDA should consistently communicate with the Sponsor well in advance of 24 hours, such as 48-72 hours in advance. Alternatively, we propose that the FDA consider rewording this section to include "a discussion and agreement with the Sponsor regarding the amount of time that would be "sufficient"" [FDA should define] prior to the first public communication that emerging safety information about its drug will be posted on the FDA web site. Such an approach will allow the Sponsor to fully prepare Medical Information staff to

	to do so)? It seems lacking and we could recommend reasons why Sponsors be given a more meaningful notice period.	answer potential queries from the public.
Lines 515-520	*"Representations that minimize the implications of emerging drug safety information communicated by FDA also may be considered false or misleading. For those seeking to explain to health care professionals what emerging drug safety information means, we refer to the sections of this guidance that discuss the purpose of disseminating emerging drug safety information and the nature of the information to be posted on the Index to Drug-Specific Information Web page."* It is important that the Agency work with the Sponsor to consider/discuss their analysis/assessment of the emerging drug safety data information that the Agency would like to communicate prior to the communication, so the Sponsor is fully prepared to address questions that may arise from Health care providers and patients.	The Agency should consider inclusion in this Guidance a timeline that allows for Agency-Sponsor interaction & discussion of the emerging drug safety information. This should include request, review and if necessary discussion with the Sponsor to fully understand and consider the signal detection work/analysis and the communication the Agency wants to release to the public. It is important for the Agency and the Sponsor to understand perspectives, and for the Sponsor to be prepared to adequately address questions from Health Care Providers and patients once the Agency communication is released.