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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Re: Docket No. FDA–2012-D-0085: Draft Guidance on Classifying Significant Postmarket Drug Safety Issues

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance on Classifying Significant Postmarket Drug Safety Issues."

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.

FDA should be applauded for providing this guidance to help FDA and industry align the way we assess our safety signals. BIO believes that the overall framework makes good sense. The process for the classification of *standard* vs. *priority* is clear. As discussed in our general comments, more examples or specific thresholds may be helpful for readers to understand the standards that FDA is going to follow in the classification of priority for significant postmarket drug safety issues.

GENERAL COMMENTS:

A. Algorithm To Identify Safety Issues:

We request a description of the algorithm used to identify safety issues. It would be helpful to know what algorithm or method of detection FDA is using, as the nature of this method will affect the number and type of issues identified. This knowledge would also allow sponsors to take into account FDA's methods when establishing their own methods.

B. Threshold for a TSI Classification:

We suggest that the guidance specify the overall thresholds that would lead a tracked safety issue (TSI) to be classified as *priority*, *emergency*, or *standard*. This knowledge would be useful in helping sponsors ensure that their internal criteria for escalation of safety issues are in line with FDA criteria. In the spirit of harmonization, and in recognition of the global nature of drug development, we further suggest that FDA consider aligning its criteria with those used by other countries' regulatory agencies (e.g. EudraVigilance Statistical Signal Detection Methods[1]).

C. "High Priority" TSI

We also note that the guidance introduces the concept of an "emergency" TSI (lines 131-133). The classifications for *standard* and *priority* TSIs are discussed at length, but the Draft Guidance does not speak to the process for classifying a TSI as an "emergency." Since most safety signals have not yet been verified at the time of TSI designation, declaring an emergency situation may be pre-mature and potentially contribute to unnecessary alarm or panic. We suggest that the term be removed or the more balanced term "*high priority*" be used in lieu of "*emergency*." If the "*high priority*" classification is adopted, we still encourage the Agency to articulate under what circumstances this classification will be employed.

D. Timelines for Acting on TSIs:

We recommend including overall timelines for FDA action on *priority*, *emergency*, and *standard* TSIs, as well as a plan for communicating these timelines to affected sponsors. Currently the guidance only alludes to further delineation of an operational framework, in the Next Steps section. The earlier sponsors are notified, the better able they will be to contribute to the assessment in a timely fashion—for example, by performing their own data analysis and informing the FDA of the results.

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[1]European Medicines Agency (EMA), EudraVigilance Expert Working Group, Guidelines on the Use of Statistical Detection Methods in the EudraVigilance Data Analysis System, June 2008, http://eudravigilance.ema.europa.eu/human/docs/26June08-GL%20on%20the%20use%20of%20stat%20meths%20signal%20detection%20EVDAS.pdf)

E. Potential Outcomes from a TSI:

We would like the guidance to specify potential outcomes from a TSI, such as asking the manufacturer to revise product labeling. We also request a better description of how FDA works with the sponsor and how that might change based on whether a TSI is classified as *standard*, *priority*, or *emergency*.

F. TSI Triggered by Similar Products:

Please specify whether safety issues of a similar product can be the basis for a TSI, and, if so, provide an example, such as hepatotoxicity of a follow-on drug where identified for a first-in-class drug.

G. Communication with Sponsors

With some TSIs, there is little to no communication from the FDA to the sponsor about the ongoing assessment (methods used, scope of the TSI, etc.) until a regulatory action is requested. In order to improve the transparency of the Agency's decisions, we suggest that the Agency discuss with the sponsor the scientific methods and regulatory action being sought. We recommend that the process be revised to include at a minimum a teleconference with the sponsor to share the Agency's findings at the conclusion of the TSI review. Even if this is not deemed feasible, sponsors must be informed, at a minimum at the time of TSI initiation, of the nature and classification of the TSI (*priority*, *emergency*, or *standard*).

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance on Classifying Significant Postmarket Drug Safety Issues." 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
I. INTRODUCTION		
Lines 19 – 20:	*"Significant postmarketing safety issues include serious adverse events, product quality issues, and medication errors."* For clarity sake it would be helpful to include examples of serious AEs, product quality issues, and medication errors, earlier in the document to set the framework.	BIO suggests that it would be helpful to include examples of serious Adverse Events, product quality issues, and medication errors earlier in the document.
II. BACKGROUND		
Lines 37 – 40:	*"To fulfill those goals, before drugs can be marketed, CDER rigorously evaluates new drug applications (NDAs) and biologics license applications (BLAs) to ensure that the benefits of the drugs exceed the risks for their intended use."* This statement makes reference to CDER's evaluation, but doesn't make it clear if other centers within the FDA would also use it.	Please clarify if this framework or classification is used, or will be used, by other centers within the FDA (*e.g.*, CBER).
Lines 75 – 77:	*"This guidance reflects one step in that process: prioritization of identified safety issues according to an established set of criteria."*	Please clarify if the Agency plans on publishing the established set of criteria for public view and comment.

	The document does not mention if the Agency plans on publishing the established set of criteria for public view and comment.	
III. TRACKING SIGNIFICANT SAFETY ISSUES		
Lines 82 – 84:	*"In January 2007, CDER took an important step forward when it launched the Document Archiving, Reporting, and Tracking System (DARRTS) module for centralized tracking of significant postmarketing safety issues."* Will the classification of significant safety issues under this guideline be made public? For example while an assessment is ongoing by the FDA, will the public be able to go online and read that the FDA has determined that there is a safety risk with x drug, that has been assigned a *priority* review?	Please clarify if the classification of significant safety issues under this guideline will be made public.
Lines 108 – 110:	*"Typically, an **interdisciplinary team** assesses the safety issue, re-evaluates the risk–benefit profile of the drug, and determines the need for regulatory action."* It is unclear who is included on the interdisciplinary team.	Please provide information on who is included on the interdisciplinary team assessing the safety issues.
A. The Next Step — A Framework for Prioritizing TSIs		
Lines 120-122:	Safety issues entered into DAARTS may initially be considered significant, but, subsequently, may be down-classified as new	Consider modifying the text at Line 115 to read: "Although all of these issues are initially considered significant…"

	information becomes available.	
Lines 120-122:	*"The Center is now seeing to establish a formal framework for prioritizing TSIs so that CDER can direct resources more effectively toward those issues posing the greatest potential risk to patients."* Will the framework under this guideline be made public?	Please clarify if the framework will be published and accessible to the public.
Lines 122 -125:	*"The use of a formal **framework** is intended to ensure that staff working in different offices across CDER have a common understanding of the relative urgency of the TSIs and direct attention to those that need to be addressed most expeditiously."* The use of the term "framework" is unclear.	Please provide definitions and examples to assist the reader in understanding the term "framework." Suggest Agency include language regarding the timing for analysis of TSI and the timely communication of any subsequent regulatory action.
Lines 131:	At Line 19 of the draft guidance, FDA establishes *priority, standard, or emergency* as subcategories of **significant** postmarketing safety issues.	For accuracy, please revise the text at Line 131 to read: "Although all significant postmarketing safety issues will continue to be thoroughly investigated …" or "Although all tracked safety issues will continue to be thoroughly investigated…"
Lines 131 – 133:	*"Although all postmarketing safety issues will continue to be thoroughly investigated, those*	Please provide additional clarity regarding what is meant by "decision making".

	deemed to be priority or emergency will be most closely monitored, tracked, and managed with clear timelines for ***decision-making****."* It is unclear to what "decision-making" refers.	Additionally, as discussed in our general comments, it seems odd to use the term "*emergency*" in this context of signal assessment and evaluation. Suggest striking the term or revising to "*high priority*" rather than "emergency."
B. Prioritization — Part of an Evaluation Process		
Lines 141-142:	"*This guidance addresses only the factors to be used to prioritize a newly identified safety issue.*" This guidance document applies to the classification of significant safety issues. Further, a significant change to the known safety issue should be within the scope.	Please add "and a significant change (e.g., severity, frequency) to a known safety issue" to the end of the sentence. "The guidance addresses only the factors to be used to prioritize a newly identified significant safety issue and a significant change (e.g., severity, frequency) to a known safety issue."
Lines 146 -148:	"*Once an issue has been prioritized, CDER staff will promptly develop and implement a plan to fully evaluate the risk and take appropriate actions, Initial activities may range from analysis of existing data to requests from the drug's sponsor.*" It is unclear at what point in time the sponsor will be notified that a "safety issue" has been identified by the agency, prioritized, and under analysis. Timely sponsor/FDA communication is critical.	We request Agency clarification regarding at what point the sponsor will be notified that a "safety issue" has been identified by the agency, prioritized, and under analysis (at time point).
Lines: 151-152	Actions taken by CDER after reaching a conclusion about a significant safety issue	Please modify the text at Lines 151-152 to read:

	might include efforts to further investigate the issue.	"Once CDER reaches a conclusion about the safety issue and decides to take action, the action may include, for example, developing additional scientific information, developing additional scientific information, requiring changes to the drug's labeling, requiring additional risk management interventions such as a risk evaluation and mitigation strategy (REMS), …"
Lines: 157-161	This paragraph describes how CDER makes decisions about appropriate regulatory action: balancing risks against benefits and the severity of the disease. However, none of the information that goes into these decisions is shared with the sponsor (or the public). So while the guidance states what the FDA does, the process and evidence leading to the decision are not transparent.	We recommend that the process be revised to include, at a minimum, a teleconference with the sponsor to share the Agency's findings. Ideally the sponsor would receive notification at the time of TSI initiation, including information about the TSI's classification (priority, emergency, or standard).
IV. METHODOLOGICAL FRAMEWORK		
Lines 169-170:	"*Staff will then examine the issue in relation to the context of the drug's use, biological plausibility, and other factors.*"	Suggest FDA change 'other' to 'modulating' and add a cross-reference. "Staff will then examine the issue in relation to the context of the drug's use, biological plausibility, and ~~other~~ modulating factors."
A. The Hazard Assessment		
Lines: 191-196	The guidance states that in assessing risk, factors such as biological plausibility, seriousness, and quality of the data will be considered, but we are concerned that a single statistic (for example, a high proportional reporting ratio (PRR)) could cause an event to	Please specify the methodology that will be used to assess risk and benefit.

	be classified as an high priority issue when in fact the data are weak or the disease has no alternative treatments. In addition to risk, is the relative/absolute benefit also taken into consideration? If the FDA wishes to avoid alarming patients, then it should consider the potential forgone benefit among patients who stop taking the drug because a TSI is issued on the FDA website, without any evidence at that point of causality.	
Lines 191 -194:	*"Once this threshold is met, CDER… based on three variables: (1) the relative seriousness of the issue; (2) the estimated size of the population exposed to the risk of the drug; and* ***(3) the suspected frequency of harm to patients exposed to the drug."*** Given that this is based on postmarketing data, there will be certain amount of underreporting.	Please clarify if "frequency" means the reporting rate of a specific adverse event in the postmarketing setting. Does the Agency plan to apply a factor to obtain a more realistic frequency of the adverse event?
1. Relative Seriousness of the Safety Issue		
Lines 198-202:	*"CDER will determine the relative seriousness of a safety issue as high or medium. In general, the seriousness will be considered high if the risk is fatal, life threatening or requires hospitalizations."* Other serious criteria such as fetal anomaly,	Please clarify whether other criteria besides those specifically mentioned in this section will be considered.

	disability, etc. are not mentioned.	
2. Estimated Size of the U.S. Population Exposed to Risk of the Drug		
Lines 212 – 221:	This section makes reference to: *"A very small percentage (3%) were used by more than 5 million outpatients within the past year, and only 11% were used by more than 1 million"* but it is unclear if this means CDER's reviewers will include only the 3% or 11% drugs that have more users when determining priority classification.	Please confirm whether CDER's reviewers will only consider the 3% or the 11% drugs for this criterion, *i.e.,* can other drugs be classified as priority based on this criterion? Can CDER provide and maintain a list of drugs meeting this criterion? Please provide reliable sources or references from which these data will be extrapolated.
Line 213 – 214:	*"A recent CDER analysis of almost 2,200 active ingredients sold throughout the US retail pharmacies shows a nearly bimodal distribution of patient exposure."*	Please confirm that only US prescription data will be used for patient exposure data.
3. Suspected Frequency of Harm to Patients Exposed to Risk from the Drug		
Lines 225 – 239:	This section refers to "*frequency of harm*" and "*a small increase in risk*" but does not provide thresholds for these items.	Please provide more specific thresholds for the combination of frequency and increase in risk.
Line 225:	*"Available information regarding the frequency of harm will be taken into account along with the context in which the drug is being used."* Same comment as for lines 191-194; this is the postmarketing setting and generally industry refers to reporting as reports for	Please clarify if "*frequency of harm*" is the same as "*reporting rate*".

	events.	
Lines: 240-244	This paragraph discusses how existing information will be used to classify a TSI when no precise information is available about the frequency of an adverse event or the risk to patients. The concept of uncertainty should be given more emphasis in the guidance.	Please describe in the guidance how uncertainty regarding the frequency of an adverse event could affect the classification of a TSI. For example, with a rare but serious adverse event, how would uncertainty factor into the Agency's decision about classification?
B. Modulating Factors		
Lines 246 – 296:	This section discusses "*other factors that have the potential to elevate or, in some circumstances, lower the classification of the safety issue*" but does not provide examples.	Recommend providing examples of how much these factors should weigh to change the hazard assessment.

1. Context of the Drug's Use		
Lines 255 – 258:	"*Considerations arising from the context of use would include, but not be limited o the following: The availability and risk profiles of therapeutic alternatives.*" The text is unclear whether or not the safety issue would be assessed across all indications (if there are multiple indications) or just the indication from the safety signal arose.	Please provide more context regarding whether or not the safety issue would be assessed across all indications (if there are multiple indications) or just the indication from the safety signal arose.
Lines 260 -262:	"*Whether the drug provides unique clinical benefits…with the same indication that are considered relatively safe and thus offer robust alternatives to patients will be considered a modulating factor.*" The term "*relatively safe*" is unclear. Also need clarification for what the comparator is, for example: an approved product.	Please clarify what threshold the FDA will use to consider an approved drug to be "*relatively safe*." Please clarify what criteria (and approved product) will be used by the FDA to determine that an alternative therapy is relatively safe.
Lines 275 -276:	"Occurrence of a serious risk in an unsupervised setting is likely to raise the level of CDER concern and make the safety issue a priority."	Please clarify or provide examples of "an unsupervised setting."
2. The Quality of the Data Suggesting the Risk		
Lines 288 – 289:	"The higher the credibility of the data, the more likely it will be considered a priority TSI."	Please clarify if the Agency stating that postmarketing reports of adverse effects will be given a lower priority than, for example, data from a targeted post marketing safety study.

	Recurrent comment (as reviewed in lines 191-194 & 225), this is in the postmarketing setting; the pitfalls of postmarketing data are widely understood.	
2. The Quality of the Data Suggesting the Risk		
Lines 293 – 296:	"CDER will consider whether there is a biologically plausible explanation for the association of the drug and the safety signal, based on what is known from systems biology and the drug's pharmacology. The more biologically plausible a risk is, the greater consideration will be made to classifying a safety issue as a priority." Many of the drugs and biologics that are currently being developed today are considered as a class if they have a comparable mechanism of action with similar adverse event profiles. Therefore it is reasonable for CDER to consider & communicate whether this information will be considered as they classify safety signals.	"CDER will consider whether there is a biologically plausible explanation for the association of the drug and the safety signal, based on what is known from systems biology and the drug's pharmacology and other drugs in the class. The more biologically plausible a risk is, the greater consideration will be made to classifying a safety issue as a priority."
V. NEXT STEPS		
Lines: 317-319	The guidance states that work plans including action milestones will be developed in order to manage safety issues. We would like to know how long it would be after an issue is identified until the sponsor is contacted, and how long the sponsor would have to respond to a high-priority issue. It could take a	Include timelines for FDA to notify sponsors of safety issues and for sponsors to respond. Address the issue of differing reference populations.

	considerable amount of time to arrive at a rational decision in some cases, particularly if the data are sparse. Also, the FDA database will have a different reference population than the sponsor's database; will this be taken into account?	