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To:

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket # 2005D-0062

Comments on FDA's "Drug Watch" for Emerging Drug Safety Information - Draft Guidance

Pharmaceutics LLC provides consulting, expert and training services to the pharmaceutical industry in the areas of Core labeling, US labeling, EU labeling, worldwide labeling harmonization, and labeling support technologies.

Our comments focus on the decision-making principles described in the draft Drug Watch guidance, and on the resulting quality of warnings posted on the Drug Watch website vis-à-vis the quality of warnings presented in drug labeling.

Understanding whether or not there is a substantial difference in the certainty threshold for inclusion of a warning in Drug Watch compared to the inclusion of a warning in labeling is important for both the public and the pharmaceutical industry.

Based on the description of the decision-making principles in the draft guidance document, there is a risk that the public (media, healthcare professionals, lay persons, other regulatory authorities) takes warnings that are portrayed on Drug Watch as "emerging safety information" less serious than warnings in labeling. And there is a risk that the terminology used in the draft guidance leads to a misinterpretation of the threshold criteria that drive the inclusion of warnings in Drug Watch, and to confusion in the scientific and regulatory community in the United States and abroad.

Before presenting specific comments, it is necessary that we briefly describe the process of safety labeling decision-making and discuss the use of the term *adverse reaction* in US and international labeling regulations and guidelines. This is not done to educate FDA about this process and US regulations. Instead, it is done to allow FDA to understand the conceptual framework and terminology (shared by many pharmaceutical industry professionals) on which we base our comments on the draft guidance.

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1. Safety warning decision-making for labeling

The most important basic element of drug safety information is the *adverse reaction*, attributed to a drug alone or in combination with other drugs/substances (adverse reaction due to an interaction).

For labeling purposes, an *adverse reaction* is to be understood as a type of undesirable event for which there is at least a reasonable possibility that it is caused by the drug (or combination of substances). For example, the EU SPC guideline states that the Undesirable Effects section should only include items that are attributed to the medicinal product with at least reasonable suspicion. In the proposed US Physician Labeling Rule, the term *adverse reaction* has been redefined to mean a "noxious and unintended response to ... a drug product for which there is a reasonable possibility that the product caused the response (...)" In one place of the proposed rule, the definition also includes an explanation of the concept "reasonable possibility"; this is discussed below.

This means:

- A. No "proof" of a causal relationship with the administration of a drug is needed in order to be able to list an item in labeling as an *adverse reaction*.
- B. Reasonable suspicion of a causal relationship, or the belief that there is a reasonable possibility that the product causes the reaction, may be sufficient to allow an item to be included in labeling as an *adverse reaction*.
- C. The items in a list of labeled *adverse reactions* are, for the most part, *suspected adverse reactions* and *not proven adverse reactions*. Using the term *adverse reactions* without the qualifier *suspected* may be considered an overstatement of the level of certainty with which many so called adverse reactions can be attributed to a product.

Labeling is, in general, not very effective in conveying the shades of certainty/uncertainty behind what is listed as adverse reactions. This is true in particular, in the European Union, where pharmaceutical companies are very limited in their ability to use any qualifiers such as "causal relationship not established" in labeling.

There are no internationally accepted rules or algorithms that determine which level or pattern of evidence should trigger reasonable suspicion, i.e. the assumption of a reasonable possibility of causation. This is not only because the type of available information and the number of factors to be taken into account may vary so widely, it is also because data and factors may be given different weights by different individuals involved in the deliberations.

Data and information may be insufficient to support a reasonable suspicion of a causal relationship, just as data and information may be insufficient to rule a relationship out. Existence of a reasonable possibility of a causal relationship is, however, not synonymous with the absence of a possibility to rule such a relationship out. The interpretation provided in one of the two versions of the revised definition of

the term adverse reaction in the draft US Physician Labeling Rule¹ is, therefore, incorrect (even if it has been taken from the ICH E2A guideline, which should be revised to correct this point). The phrase "reasonable possibility that the product caused the response" would be better described as "a possibility assumed based on credible data and/or plausible arguments that suggest a causal relationship".

The subjectivity of the decision when to warn about a risk is further increased by the decision makers' compliance with the expectation of the users of a product (patient, consumer, healthcare professionals) to be warned the sooner (i.e. at a lower level of certainty about a causal relationship) the more relevant the risk under discussion is.

The relevance of a risk for a patient/consumer is a function of subjective factors (such as individual risk-acceptance) and non-subjective factors such as the seriousness of the potential reaction, its transmittability, its irreversibility, the probability of its occurrence, the availability of safer or more effective therapeutic alternatives (see also the threshold-lowering criteria listed in the CIOMS III/V report). Individuals or committees charged with deciding if the time has come to warn about a possible risk will take these factors into account, and the individual experiences, values and risk acceptance (as potential patients/consumers) of the decision makers will influence at which level of certainty they act.

The situation described above explains why different individuals or committees, based on the very same data and information, may arrive at different decisions about the appropriateness to warn.

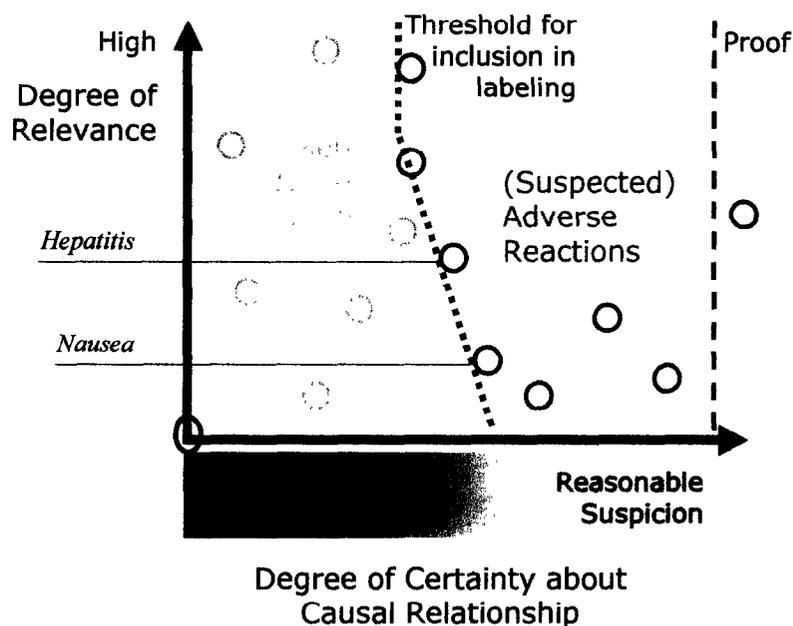
It has also to be acknowledged that a decision to *warn* about a risk may be taken at a lower level of certainty about a causal relationship than a decision to *take a product off the market*. This is not in the least because the decision to stop marketing may withhold benefit from patients/consumers who would not experience the adverse reaction.

The underlying degree of certainty about the existence of a causal relationship varies from adverse reaction to adverse reaction listed in labeling. Often, certainty will be lower for serious or otherwise very relevant items, and it will be higher for less relevant items. This is not the result of an intentionally heightened threshold for less relevant items, but the result of the lowering of the threshold for more relevant items, which may, if very relevant, even be included very early - as long as the decision makers don't consider it non-reasonable to suspect/assume a causal relationship. And even then, they are formally classified and addressed as (suspected) adverse reactions.

The Figure shown below illustrates (with all the limitations of diagrams for such complex concepts) how the threshold for inclusion of safety items in labeling shifts to the left (towards a lesser degree of certainty) for more relevant items. That the threshold turns vertical and will never intersect the relevance axis means that an item, even if extremely relevant, will not qualify as an adverse reaction if it is not reasonable to consider causation by the product a possibility. The diagram also shows a "grey zone" between absence and presence of reasonable suspicion. While

¹ "An adverse reaction is a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response (i.e. the relationship cannot be ruled out)." (Emphasis added)

an individual may not experience such a grey zone, committees often experience that some of the members have already arrived at the point of reasonable suspicion, while others have not. In such a situation, it is much easier to arrive at a unanimous decision if the dimension of relevance is taken into account.



The inclusion of an item as a suspected adverse reaction in labeling (possibly along with advice to take precautionary measures) is often only an early precautionary step in the context of a continuing effort to determine "whether an *actual* safety problem exists" (using a phrase from the draft guidance). So will items that have crossed the threshold for inclusion in labeling based on reasonable suspicion occasionally have to be reclassified to "mere events" when more information emerges - although this does not mean that a pharmaceutical company will always be successful in removing them from labeling (regulatory authorities may disagree; subjectivity).

It should be noted that the criteria described above do not usually apply to the lists of items that are presented (typically in a tabular format) in an US Adverse Reactions section to represent adverse experiences from clinical trials. While such tables are sometimes misleadingly called adverse reaction tables they reflect, if at all, only the investigators' causality assessment. This means that they do not reflect the pharmaceutical company's or FDA's end-of-development-phase causality assessment (taking into account all available data at the end of clinical development). Which of these items are considered "true" adverse reactions (by company and FDA) can often be seen in the Warnings and Precautions sections, where serious and relevant suspected reactions are discussed.

2. Comments on the draft Drug Watch guidance, suggestions

While the draft guidance uses different terminology, the overall decision-making framework that it describes for posting items on Drug Watch appears to be very similar to the framework for labeling.

- A. In the Q&A document accompanying the draft guidance, the term "emerging risk" is defined as "possible serious new side effect", which translates into "suspected serious adverse reaction". Consistent with this definition in the Q&A document, the draft guidance appears to use the term "emerging risk" as quasi synonym to "serious side effects [that] emerge" (lines 31,32).
- B. An "emerging risk" is contrasted to a "real safety concern related to the drug" (line 34, 35). The phrase "known with greater certainty" (line 40) appears to say that "proof" of a causal relationship may not be a requirement for considering an item a "real safety concern related to the drug". There is no equivalent term in the labeling model presented in section 1. In labeling, *adverse reactions* are usually not formally sub-classified based on the underlying level of certainty. Rather, a relatively high degree of certainty may be conveyed by the use of more affirmative language like "PRODUCT causes the following adverse effects ...". Lower levels of certainty may be found conveyed by qualifiers such as "causal relationship not established" or by disclosing the limited information available.
- C. The draft guidance also addresses the minimum requirements for an item to be posted on Drug Watch. One criterion, which is not expressly stated but implied throughout the document, is that causation is at least considered a possibility. A second criterion is that, based on at least a preliminary analysis of available information, it is determined "that the new safety information is sufficiently credible to warrant public dissemination" (lines 167-169; underlines added). Both criteria together can be considered to represent determination that "causation is a *reasonable* possibility".
- D. The proposed procedure is also consistent with the practice of warning sooner if the item is more relevant. This is already reflected in the overall objective of the initiative: information about serious new risks will now, in a consistent manner, become actively disseminated by FDA at a lesser degree of certainty than before. The draft guidance does not address the question whether or not the Drug Safety Oversight Board would apply a lower threshold for serious or otherwise very relevant items compared to less relevant items. Making such a distinction would, however, be irrelevant because the focus of the initiative is only on *serious* new risks.

Overall, the decision-making criteria and rules for the Drug Safety Oversight Board appear to be remarkably similar to the criteria and rules expected to be used and followed by pharmaceutical companies when deciding whether to include information about new risks in labeling:

Items that are serious/relevant for therapeutic decision-making may be posted on Drug Watch even if there is not more than a reasonable suspicion or a reasonable

possibility that they are caused by the product. However, items will not be posted if there is no reasonable suspicion that they are caused by the product.

If this conclusion is *not correct*, i.e. if the Drug Safety Oversight Board plans to always or occasionally post safety information even if it sees no reasonable possibility that the risk is causally associated with the product, then this should be clearly stated in the guidance. If it is planned to post such information only on an exceptional basis, while normally posting information when the reasonable possibility threshold has been reached, the guidance should state how "sub-threshold" information would be differentiated from other information (e.g. by means of standard qualifiers).

If this conclusion is *correct* (our assumption on which we base the following comments), then the quality of risk information posted on Drug Watch is not substantially different from the quality of many safety warnings published in labeling. That the Drug Safety Oversight Board might arrive at a decision to warn about an item earlier than a pharmaceutical company, i.e. before a company includes the item in labeling, may happen as a result of a difference in available data, or simply because of the significant subjective element in decision-making.

Via Changes Being Effected (CBE) supplements, pharmaceutical companies are allowed to strengthen safety information in labeling, and publish new safety warnings, without prior approval by FDA. FDA appears to be creating an equivalent mechanism for the agency and the Drug Safety Oversight Board to go public with safety warnings without prior agreement with the affected pharmaceutical companies.

Having the FDA and the pharmaceutical industry, without prior coordination, publish potentially different sets of "new risks" in independent media (Drug Watch; company websites, labeling) increases the complexity of the system for the public.

Our suggestions:

1. We suggest that the guidance use established regulatory terminology ("reasonable possibility that a product causes the effect" etc.) in describing the factors driving a decision to post information on Drug Watch. These terms can then be explained and illustrated by examples to make them accessible to the general public and the medical community.
2. We suggest that FDA also mentions that the decision making criteria for posting information are substantially identical to the criteria to be followed by the pharmaceutical industry, and that any discrepancies between information on Drug Watch and in labels may, among other things, be a consequence of the inherent subjectivity of such decisions to warn.
3. The guidance should also make clear that, in many cases, pharmaceutical companies will be the first to warn about new risks, and that the Drug Watch website should not be understood to be the primary location for finding new risk information.

4. The Drug Watch site should have a disclaimer advising visitors of the value of labeling as a tool for publishing new risk information that may not (yet) be covered on Drug Watch, and the site should have links to lead visitors to the most current label.
5. A solution that reduces complexity for the general public could be a web site where both the Drug Safety Oversight Board and pharmaceutical companies post new risk information that has not yet been agreed upon between FDA and companies. Such a nationwide single point of access to pharmaceutical risk information could also include a list of recent agreed-upon safety labeling changes. All information on such a site could be linked to SPL and be accessible from all web sites and computer systems that provide the SPL(s) for the affected product(s).
6. In the context of the Drug Watch initiative, FDA should enter a dialogue with the pharmaceutical industry and other stakeholders about a consistent way of qualifying safety information as preliminary, where appropriate. This could even have a beneficial effect on labeling policies worldwide and, in particular, in the European Union.

Sincerely,



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