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October 14, 2003

Food and Drug Administration
Dockets Management Branch (HFA-301)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**SUBJECT: Proposed Safety Reporting Requirements for Human Drug and
Biological Products
Docket No. 00N-1484 Issued March 14, 2003**

To whom it May Concern:

We applaud the Agency's initiative to improve the safe use of human drug and biological products. We understand that many of the provisions in the proposal were developed jointly by innovator pharmaceutical and biologic industry and regulatory authorities in the United States, the European Union, Canada, Switzerland and Japan to improve the quality and consistency of safety information being reported to regulatory authorities globally.

Many of the provisions that have been included in the proposal will improve the quality of safety reporting and some issues we seek your clarification.

We have reviewed the proposed guidance issued on March 14, 2003 and have the following comments and questions:

Harmonisation

In many issues it seems that the Proposed Rule is not in harmony with the ICH guidelines.

Suspected Adverse Drug Reaction (SADR)

The definition of SADR, "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". In this definition, the phrase 'a reasonable possibility' means that the relationship cannot be ruled out.

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For all spontaneous reports 'Implied Causality' applies, all spontaneous reports are considered 'related' for reporting purposes.

For the reports received from clinical studies, this may lead to companies reporting all events whether considered 'Related' or 'Not Related'. This will increase the amount of reports that the FDA will receive. This will also increase the amount of study reports to other Regulatory Authorities, as for the consistency of the data, usually only one international assessment of relatedness for a case will be made. In case of different relatedness-assessments for different countries a problem will be faced when gathering the data into one single PSUR.

In a double-blind study, blinding of the study is endangered, if the code needs to be opened for regulatory reporting purposes more frequently due to the above effects on the causality assessment. However, in a clinical study this will not make the expedited reporting more medically meaningful. The data in the clinical study including safety will anyway be analysed statistically at the end of the study and in possible interim analyses.

SADR With Unknown Outcome

“If the outcome for an SADR is not known, a determination of seriousness cannot be made; the SADR would not default to a "nonserious" designation, but would rather be classified as an "SADR with unknown outcome".

What kind of 'status' will the reports classified as 'SADRs with unknown outcome' have?

According to the ICH a report is classified as 'Serious' or 'Non-serious', which is one of the criteria for a report to be submitted to the Regulatory Authorities. An additional third category would cause problems e.g. in the electronic submission of reports (E2B) throughout Europe. It will be very likely that the companies will upgrade these 'SADRs with unknown outcome' to be 'Serious' to enable a fluent workflow of the reports worldwide. This could again lead to more reports being submitted to the Regulatory Authorities and more reports to be included in the PSURs and maybe in some cases, cause a skewed picture of the data received.

This will be technically very difficult to handle for many companies operating globally, as in EU the reports are categorised either as 'Serious' or 'Non-Serious'. The different reports are also difficult to handle in various listings, PSURs etc.

What evidence does the FDA require the companies to have of those reports that will remain with an unknown outcome?

Full Data Set

Completion of all the applicable elements on FDA Form 3500A (or on a CIOMS I form) including a concise medical narrative of the case.

What is the definition of 'applicable elements'?

Active Query

Under the proposal, the term "active query" to mean, "Direct verbal contact with the initial reporter of a suspected adverse drug reaction or medication error by a health care professional. For SADRs, active query entails, at a minimum, focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR.

Quite often it is very difficult to get in touch with e.g. a hospital-physician by telephone. The physician may not have the patient's data at hand. Companies starting to phone concerning each individual report may lead to the fact that the physicians stop reporting SADRs as they might regard the reporting too time consuming. Potential misunderstandings at both sides may cause misleading information, and clarifications are difficult to trace. E-mail or written letter questioning would, in many cases, be a better solution for getting follow-up information.

Supporting Documentation

The supporting documentation is difficult to obtain in many countries according to local legislation etc. Some authorities will not generally release supporting documentation to companies, even if they would have it and they would in many cases not provide any further and relevant information to the case.

How would these documents be handled and submitted electronically?

Contractors and Shared Manufacturers

The exchange of information between companies within five (5) days is very often difficult to arrange, if it is a requisite that the 15-Day timeframe for regulatory reporting starts here.

Lack of Efficacy reports

For example, applicants would be required to submit information concerning reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease.

What is the definition of a 'serious disease'?

Always Expedited Reports

How will the FDA keep the companies informed about the new, added events that are subject to 'always expedited reports'?

This should be clearly provided somewhere and if possible, the list should be updated with a periodic interval known to all relevant parties.

Reporting Requirements

The different timeframes for differently categorised reports are not in line with the ICH and will cause trouble in companies operating worldwide. The processing of individual reports will become difficult to handle in various databases built for the 7/15 calendar days in handling of the reports.

It is recommended that the reporting intervals for the Periodic Reports and PSURs should be following the ICH guidance, i.e. the same as in the EU. If not, it will require extra work for the companies for preparation of the US specific reports not existing in the EU and thus discard the idea of harmonisation.

Contact Persons

The contact person for a company should be U.S based due to the time differences. The safety documents, however, are mainly located in Europe for Europe-based companies.

Physician rule

Orion Pharma is a Finnish pharmaceutical company and we would like to know if a non-U.S. licensed physician would be able to evaluate safety information? Would it be sufficient to have a licensed physician in the foreign headquarter of the company and a local representative for FDA contact in the US?.

We would appreciate your reply to the above questions and comments.

Sincerely,



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