TRIMERIS

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10 October 2003

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher's Lane Rm. 1061
Rockville, MD 20852

Re: Docket No. 00N-1484: Proposed Rule - Safety Reporting Requirements for Human Drugs and Biologic Products (Federal Register/Vol. 68, No. 50/Friday, March 14, 2003 and Federal Register/Vol. 68, No. 117/Wednesday, June 18, 2003)

Dear Sir or Madam:

Trimeris Inc. welcomes the opportunity to submit comments on the Food and Drug Administration's ("FDA's") proposed rule entitled "Safety Reporting Requirements for Human Drugs and Biological Products." FDA released the document on March 14, 2003 "to implement definitions and reporting formats and standards recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's (WHO's) Council for International Organizations of Medical Sciences (CIOMS)" for worldwide consistency, increased quality of safety reports and expedited FDA review of critical safety information as well as continued protection and promotion of public health.

Trimeris Inc. supports FDA's efforts to harmonize safety reporting standards. We offer the following comments and requests for clarification for your consideration.

Section II.B.4 Bioavailability and Bioequivalence Studies Not Subject to an Investigational New Drug Application (IND)

Current Regulation – Human bioavailability and bioequivalence studies that are not being conducted under an IND (under Title 21 Code Federal Regulations (CFR) § 320.31) are only required to comply with the IND requirements of part 312 for certain products or certain types of study.

FDA Proposed Regulation – FDA is proposing to amend the current regulation to require expedited safety reports for serious, unexpected adverse experiences (SADRs) as prescribed under §312.32.

Comments – Trimeris concurs with the FDA's proposed regulation. However, Trimeris requests clarification regarding bioavailability and bioequivalence studies that are conducted by U.S. sponsors outside of the U.S. and not conducted under an U.S. IND.

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Section III.A.2 A Life-Threatening SADR

Current Regulation – Title 21 CFR § 312.32(a) defines a life-threatening adverse drug experience as follows:

> Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

FDA Proposed Regulation – FDA proposes to add the phrase "or sponsor" after the word "investigator" thus allowing the sponsor to have an opinion in severity of the adverse drug experience.

Comments – Sponsors tend to be conservative in their approach to reporting adverse events but sponsors lack the benefit of having the full knowledge of the subjects' adverse drug experiences; whereas the investigator is at the bedside of the patient. Although FDA acknowledges there may be discordant opinions between the investigator and sponsor, Trimeris believes allowing a sponsor to determine severity will change the nature of the assessment of life-threatening reactions and result in increased reporting of events assessed by those with often incomplete information on which to base decisions.

Section III.A.5 Minimum Data Set and Full Data Set for an Individual Case Safety Report

FDA Proposed Regulation – "The blind should be broken for each patient or subject who experiences a serious, unexpected SADR unless arrangements have been made otherwise with the FDA review division that has responsibility for review of the IND."

Comments – Trimeris believes that for small trials, especially in life-threatening illnesses with substantial morbidity, that breaking the blind in all instances of serious, unexpected SADRs could introduce bias into the study. However, Trimeris acknowledges that in certain instances it is absolutely necessary for treatment and safety of an individual subject to break the blind. Trimeris recommends that FDA consider utilizing the wording of the ICH E2A guidance by replacing "the blind should be broken" with "it is recommended that the blind be broken."

In response to the FDA's consideration of whether the blind should be broken for other (e.g., expected) serious SADRs, Trimeris believes that unblinding of other serious SADRs could also compromise the integrity of a study. Currently, if a safety signal is observed, sponsors are obligated to unblind studies for individual subject cases.

Section III.B.2 a Minimum Data Set

FDA Proposed Regulation – FDA proposes to amend 21 CFR § 312.32(c) "to state that sponsors must not submit an IND safety report for an SADR to the agency if the report does not contain a minimum data set (i.e., identifiable patient, identifiable reporter, suspect drug or biological product and SADR). If a minimum data set is not available, a sponsor would be required to maintain records of any information received or otherwise obtained for the SADR along with a record of its efforts to obtain the report."

Comments – Trimeris would like more clarification as to the specific definition of an identifiable patient and identifiable reporter, as components of the minimum data set.

There are instances in which the FDA's defined minimum data set will not be available. Trimeris is concerned that maintaining records of efforts to obtain such information will become an unnecessary administrative burden on sponsors. In addition, Trimeris would like clarification as to the timeframe for such record keeping.

According to FDA's definition of an SADR, "a reasonable possibility" must exist for "a noxious and unintended response" to be classified as an SADR. It has been the experience of Trimeris that causality is not always immediately known or determined for such experiences. Trimeris is concerned that waiting for collection of all elements of the minimum data set, especially determination of causality, could result in significant delays in reporting such experiences to FDA. For instance, telephone safety reports could take more than 7 calendar days to get all necessary information. Currently the reporting time clock starts as soon as any person in the sponsor's employ is notified of the occurrence of "a noxious and unintended response to any dose of a drug product." Trimeris would like clarification as to when the reporting time clock would start for instances in which causality or another element of the minimum data set is unknown. In addition, Trimeris believes this rule could be interpreted differently by different sponsors.

Section III.B.5 Investigator Reporting

FDA Proposed Regulation – "An investigator must report to the sponsor any serious SADR (as defined in § 312.32(a)) immediately and any other, SADR (as defined in § 312.32(a)) promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR."

Comments – Trimeris would like more clarification of "immediately" and "promptly."

We appreciate the opportunity to submit these comments. Please feel free to contact us if you have any questions.

Respectfully Submitted,

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TRIMERIS INC.