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October 14, 2003

Division of Dockets Management (HFA-305)
[Docket No. 2000N-1484]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir/Madam:

The College of American Pathologists (CAP) appreciates the opportunity to comment on the Safety Reporting Requirements for Human Drug and Biological Products proposed rule published March 14, 2003 (FR 68:12406) (Docket No. 00N-1484). The College represents more than 16,000 pathologists who practice medicine in community hospitals, academic medical centers, independent laboratories, and other health care facilities. Pathologists are the medical directors of blood banks in hospitals and have a great interest in blood reporting and blood products safety.

The proposed rule would implement definitions and reporting formats and standards for human blood products reporting. The CAP supports continued quality and safety improvement in the blood product collection and manufacturing processes, and in the subsequent clinical use of these products. Additionally, the concept of having more consistent, and complete collection of reports of serious errors in these areas is important.

However, the College believes more precise definitions of the terms in the proposed rule is needed to accomplish the goal. The College would define serious errors as those errors which could, or do, cause harm to patients, and even if only potential, have slipped through the first level of safety checks. Further, the CAP believes that more consistent information concerning serious adverse reactions due to blood transfusion, whether or not related to error, is important for new knowledge about the biology of transfusion, and ultimately patient safety. However, the transfusion process is part of the practice of medicine, and issues of error and/or substandard practice are traditionally handled in nonfederal forums, and are beyond the scope of the agency. The attempt in the proposed rule to collect broad, ill-defined reports and then categorize them, may as a consequence not achieve the results the Food and Drug Administration (FDA) desires.

The FDA has laudable expertise and knowledge about the sciences of both blood products themselves, and issues in their manufacture. However, as a group, transfused patients are the sickest and most complex patients, frequently with multiple illnesses. For example, the six-month survival of transfusion recipients identified as part of hepatitis C look back was

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only 60% (Vamvakas EC, Goldstein R. Transfusion 42:691, June 2002). In this case, death was due to the patients' underlying illnesses, rather than the transfusions. Often delineation of the relation of a patient's morbidity to a concomitant transfusion amidst multiple other medications and therapies, demands years of clinical experience in these settings.

The proposed rule implies transfusions take place in an isolated manner with the pharmacological agent of the blood product being the only variable. Such can be the case, but is often not so. Additionally, in some regards, there is an implication of required reporting of what could be interpreted as "off label" use, again an area traditionally within the purview of individual physicians. Should more consistent review of practice be needed, rather than the current proposed rule, it would be more appropriate for the Centers for Medicare and Medicaid Services (CMS) to require hospital systems for such review as part of institutional Medicare accreditation, with individual case reporting to an independent group (as described later).

In addition to an unwarranted move into medical practice, the proposed rule has certain defects and ambiguities, which could place a significant burden on hospitals and other transfusion services, as well as being likely to overwhelm the agency with reports. The estimated number appears quite low, given the broad, loosely defined requirements.

The proposed definition of a serious adverse drug reaction is: "A noxious and unintended response to any dose of a drug [or biological] for which there is a reasonable probability that the product caused the response." In this definition, the phrase "a reasonable probability" means that the relationship cannot be ruled out (p. 12417). For patients with complex illnesses, there are few cause and effect relationships, which can be ruled out. For example, the agency lists items such as congestive heart failure and metabolic imbalance. In patients with not only multiple illnesses, but also perhaps dozens of other medications, it can be virtually impossible to include or exclude relationships with congestive heart failure.

The phrase "metabolic imbalance" is also not well defined. All patients who are transfused with large volumes of blood have at least transient metabolic imbalance, even without complicating illnesses. Clearly, a metabolic imbalance such as a sudden fall in ionized Ca temporally coincident with a large volume of citrate containing blood is related, or in such an instance if the bloodline were in the right atrium, a causal relation to a temporally coincident arrhythmia would be reasonable. However there are many changes in patients which are most likely not due to transfusion, are not "reasonably possible", but wherein transfusion cannot be ruled out. If this rule is issued, a standard of "definite" or "confirmed" should be substituted. Even "likely" or the more usual uses of "reasonably possible" are subject to ambiguity. Terms such as "confirmed" or "more likely than not" are greatly preferred.

The two categories of induced alloimmunization are confusing. The reportable category only lists post transfusion purpura as an example (e.g.), meaning other types of cases are also reportable. Presumably then all patients with reduced platelet increments due to HLA

or anti-platelet antibodies must be reported, since reduced increments do impact care. Similarly, all instances of red cell alloimmunization to so-called "minor" antigens such as Kell, Kidd, cCeE, etc would have to be reported, even though medical error would not have been involved in the immunization. However the alloimmunization does impact care and cost and would seem to require reporting under the rule. The nonreportable cases are ones wherein there is not an impact on care. For red cells there would need to be better definition of what antibodies are incidental, and what are not. Even such a distinction in a patient can impact care, by delaying a transfusion until it is known that the detected antibody is not clinically significant. With platelets the relation between antibody and clinical impact in a specific patient is more difficult to determine, given other clinical factors that adversely affect in vivo yield. The definitions of, and exclusions from, SARs on page 12436 are not clear or precise, so that what is reportable and non-reportable is not easily discerned, even without the difficulty in causality (see above).

The meaning of medical intervention is unclear, as implied previously. In a patient with marginal cardiac status, slowing the rate of transfusion is an intervention. Rejecting an antigen positive unit for a patient with anti Kell, and going through the cost and delay, of finding a Kell negative unit is an intervention. Also, having to give extra platelet doses because of reduced yield, due to the patient's primary illness, can be an intervention.

The agency grossly underestimates the volume of cases that will be reported, as well as the cost impact on transfusing institutions. There would have to be some variety of financial support to hospitals for the activity. Further, the agency itself would not have staff sufficient in numbers and training, to process the information. This is also true for the field inspectors, who presumably would examine hospital records to see if all reportable cases had been reported. An unstated factor is that the reports would become public record. If on the basis of these ill-defined terms hospitals are forced to report cases wherein as in volume overload, the effect of transfusion "cannot be ruled out", they will become targets for specious litigation based on their own seeming judgments.

The MedWatch Form 3500A proposed for reporting is a generic form for medical device and medication reports. Transfusion problems would be reported in free-text format. This would render the reports so variable in content that their value for analysis would be dubious.

If a comprehensive reporting system of serious adverse events not related to manufacturing is needed, then it should be through a respected professional, nongovernmental group, with clear definitions of serious events requiring substantive intervention, and with a well-designed instrument for transfusion data collection, separate from other medications. Alternatively, even within the federal government, there are other agencies more directly involved with monitoring clinical care than the FDA. The Agency for Healthcare Research and Quality has a charge, which is more consistent with the desire for greater understanding of transfusion errors and related serious adverse events. This latter agency is better able to call on experts to formulate clearer focused criteria for reporting. Further, there should be adequate confidentiality protection for the reports.

The College wishes to continue to work with the agency improve on the consistency in the collection of safety information and submission of safety reports and protect and promote public health. Any questions about this comment should be directed to David Mongillo, Director of Professional and Regulatory Affairs, 202-354-7110, dmongil@cap.org.

Sincerely,

Mary E. Kass, M.D.

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President