THE CLEVELAND CLINIC FOUNDATION

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Dockets Management Branch (FHA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule
21 CFR Parts 310, 312, 314, 320, 600, 601, and 606
[Docket No. 00N-1484]

Dear Docket Manager:

The Cleveland Clinic Foundation (CCF) respectfully takes this opportunity to comment on the proposal of the Food and Drug Administration to amend current safety reporting for human biological products. The CCF is a large, tertiary-care hospital and outpatient center in northern Ohio. More than 1,100 physicians practice in this hospital of nearly 1,000 staffed beds. Hospital admissions average 52,000 per year, and there are more than 62,000 annual surgical procedures. Our transfusion experience of 140,000 units of blood and blood components each year is greater than any other hospital of which we know.

The specific portion of the Proposed Rule (PR) of concern to us is that which relates to blood and blood components [Parts 600 ff.] Currently the agency requires reporting of fatalities **confirmed** (emphasis added) to be due to blood transfusion [21 CFR 606.170(b)]. The extensive, additional reporting requirements in this PR would, as written, overwhelm our current resources with new regulatory burdens.

The useful, current phrase "confirmed to be fatal" in 21 CFR 606.170(c) is proposed to be replaced with "if the fatality is related to transfusion". In its preamble to the PR the agency foresees no increase in the number of fatalities to be reported (page 12467). However, the PR also defines a new term, "suspected adverse reaction" (SAR). The regulation would now pertain to a "SAR that results in a fatality". Further, a transfusion reaction qualifies as a SAR if there is "a reasonable possibility" that the product caused the reaction. The PR is explicit that "a reasonable possibility" means that the relationship cannot be ruled out [proposed 21 CFR 600.80(a)].

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The implication of this is staggering. In the preamble to the PR the agency lists congestive heart failure, cardiac arrhythmias, respiratory insufficiency, bacterial infection, and other conditions as examples (page 12436). Blood transfusion is a therapy we provide to the sickest patients in our hospital. Many transfused patients have cardiac problems or are in respiratory distress. The extended differential diagnosis of such problems often includes complications of blood transfusion. Although it may not have been the intent, the literal expectation is that hospitals report every death of a transfused patient whenever a relationship between the transfusion and the death could not be ruled out. **The phrases "reasonable possibility" and "relationship cannot be ruled out" must be stricken from the Final Rule and replaced with the current and reasonable standard of "confirmed".**

In addition, the new 21 CFR 606.170(b) would require reporting of every "serious SAR" related to transfusion. In the preamble to the PR the agency says this includes any reaction that "requires immediate medical intervention or follow up medical attention" (page 12436). The agency estimates that this will generate only 7,000 reports per year (page 12471), even though a literal interpretation would require hundreds of thousands of reports of non-fatal events. This implication is obvious when one combines the inclusiveness of "a relationship cannot be ruled out" with "requires...medical attention". Every transfusion temporally associated with dyspnea, fluid overload, fever, infection or rash would generate a report. **The Final Rule must strike the same phrases as described above and replace them with the reasonable standard of "confirmed" to be due to blood transfusion.**

Further, all suspected but non-serious SAR's will also have to be studied, recorded for internal use, and the records made available to FDA investigators during their routine and periodic inspections of our hospital transfusion service. A new team of recordkeepers will be needed to comply with the letter of the Rule as proposed. **The onus would be reasonable were the agency explicitly to minimize the recordkeeping and reporting to only those cases which, in the opinion of an experienced physician, were clearly due to blood transfusion.**

The requirements of the PR are in addition to Biological Product Deviation Reporting, which the agency instituted in 2001. The release of every blood component that does not meet standards of purity, potency, or efficacy must also be reported to the FDA [21 CFR 606.171]. Units that do not meet such standards and lead to a suspected SAR would be reported twice to the same agency under the PR.

The expense to our hospital will be enormous if the Rule goes into effect as proposed. The agency's estimate of the costs of compliance is impossibly low. The assumption that hospitals are already preparing all such reports for internal use is invalid. Even if the wording of the reporting requirements were restricted to those reactions that are confirmed to be transfusion-induced, the costs will still be far greater. Many more hours go into any report for external regulatory consumption than are needed for an internal quality assurance purpose. The proposed reports will become public record. They will increase a hospital's liability to allegations of medical malpractice.

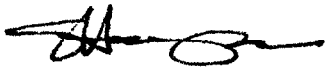
What impact would the Rule as proposed have upon the workload at our hospital?

- We currently report fewer than 0.3 fatalities per year to the FDA. There were 1,287 deaths at our hospital in 2002. At least half of these patients were transfused. If even 10% of these cases (a very conservative estimate) met the expanded definition of the proposal, **more than 60 fatalities** would be reported annually under 21 CFR 606.170(c).
- We transfuse about 75 patients per day. All of these patients have complicated medical conditions. If even 5% met the definition of a serious SAR (again, a very conservative estimate), **more than 1,300 cases** would be reported annually under 606.170(b).
- The proposal would require all non-serious SAR cases to be investigated and data retained for possible review by an investigator. Every transfusion would have to be investigated to determine whether a potential SAR condition exists, *i.e.*, **chart reviews of more than 12,000 patients** per year would be required.

Regardless of the details in the Final Rule, the FDA expects facilities to follow Good Manufacturing Practices without error. No aspect of GMP is insignificant. It is clear that these FDA requirements will not be met in our hospital with existing resources. We estimate the costs of compliance to be in the many hundreds of thousands of dollars per year. We remind the agency that no financial compensation is available for such a mandate. All administrative resources needed for this Rule would have to be transferred from direct patient care. Our patients would suffer rather than benefit.

We respectfully request the agency to adopt each of these changes in its formulation of a Final Rule.

Sincerely,



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