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

Re: Docket No. 01D-0221

Dear Sir/Madam:

We are writing on behalf of a leading manufacturer of biotechnology products with comments on the Draft Guidance published on August 13, 2001, by the Center for Biologics Evaluation and Research ("CBER"), titled "Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components" (Aug. 2001) (the "Draft Guidance").

By way of background, on November 7, 2000, the Food and Drug Administration ("FDA") published a final rule amending the regulations for reporting errors and accidents ("deviations") in the manufacturing of biological products. 65 Fed. Reg. 66621. Under the final rule, a manufacturer must report biological product deviations that "may affect the safety, purity, or potency of a distributed biological product." 21 CFR 600.14(b)(1). In the preamble to the final rule, the agency stated that it would provide additional guidance to industry concerning what constitutes a reportable deviation for purposes of the "may affect" standard in the final rule. 65 Fed. Reg. at 66624.

The Draft Guidance, however, largely restates the reporting requirements under the final rule. It provides little in the way of new information or meaningful instruction for deciding whether a given event is reportable or non-reportable. There is, for example, no discussion of the factors that should be considered in determining whether a given event "*may* affect the safety, purity, or potency of that product" for purposes of the final rule. Without some level of specificity from the agency, manufacturers will be forced to over-report, for fear of violating the final rule. Over-reporting, however, is contrary to the goal of streamlining the industry's reporting obligations by focusing only on deviations directly associated with a public health risk. 65 Fed. Reg. at 66622 ("FDA is also

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narrowing the scope of the reporting requirement . . . to those reports that are necessary to protect the public health . . . .").

Second, in at least one instance, the Draft Guidance appears to override and significantly broaden the reporting standard found in the final rule. On page 9 of the Draft Guidance, question 2a, CBER states that "*any change* from the validated manufacturing process that would prevent a product from meeting *all* Current Good Manufacturing Practice (cGMP) requirements" is *per se* to be considered a reportable event. The final rule, however, limits reporting only to those cGMP deviations that "may affect" product safety or quality – *i.e.*, only to those deviations that are also specifically found by the manufacturer to have the potential to affect product safety or quality. Question 2a must be rewritten to conform to the final rule, to give meaning to the agency's determination in 21 CFR 600.14(b)(1) that some cGMP deviations do not meet the standard for a reportable event.

Finally, we ask FDA to confirm that the final rule is not being interpreted to require manufacturers to report findings from all internal audit reports and from all audits conducted by clients and contractors that have identified potential or actual cGMP deviations. Moreover, we urge FDA to confirm that, in implementing the final rule, CBER will not attempt to begin seeking access to such reports. By conducting audits, companies demonstrate interest, concern and diligence in controlling quality, preventing errors and identifying areas for improvement. However, many audit findings are relatively insignificant and do not raise concerns about the quality, purity, effectiveness or safety of the product. Other findings may illustrate potential weaknesses or only raise potential deviation issues. We are concerned that the reporting requirements not negate the intent of audit programs or otherwise create a disincentive for manufacturers to be as comprehensive as possible in their internal audits. Failure to clarify that such reports remain outside the scope of the final rule may create a reporting burden not accounted for in the agency's own analysis. *See* 65 Fed.Reg. at 66630 (FDA arguing that manufacturers will be doing *less* reporting under the amended regulations).

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Based on the guidance offered by CBER (and the lack thereof), we are concerned that CBER has effectively broadened the agency's intent with respect to the types of deviations that must be reported under the final rule. In implementing the final rule, it is important for CBER to provide manufacturers with meaningful and instructive guidance – through specific examples or a discussion of the relevant

factors – on how to determine whether a given event must be reported. Moreover, to the extent that almost any deviation in a manufacturing process could, in some indirect way, be characterized as affecting the quality of a product, it is imperative that the standard in the final rule be applied in a reasonable manner.

Only through appropriate implementation can it be assured that the final rule will serve the goals behind the reporting of product deviations, including enabling FDA to respond to public health risks in a timely manner. 65 Fed. Reg. at 66623. Over-reporting of deviations by manufacturers, based on uncertainty over the "*may affect*' standard, will only increase the agency's monitoring burden and decrease its ability to identify and respond to genuine public health risks. Moreover, as stated in the preamble to the final rule, the agency's intent in amending the product deviation reporting requirements was, among others, to relieve industry from some of its reporting burdens by *narrowing* the scope of the reporting requirements to those that are necessary to protect the public health. *Id.* at 66622. Without adequate guidance, the agency will in effect have established a standard that is so broad it will no longer be a meaningful tool in determining whether a product deviation report is, or is not, required. The unfortunate result under those circumstances may be to actually *increase* the reporting burden of manufacturers.

Thank you, as always, for the opportunity to provide comments on the agency's draft guidance documents.

Sincerely yours,

HOGAN & HARTSON L.L.P.

Robert P Brady

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