807. A manufacturer or an initial distributor of an imported blood culturing device that has already begun commercial distribution under the existing exemption from premarket notification is required to submit a premarket notification on or before October 25, 1995 and must have a premarket notification cleared by FDA by April 22, 1996.

FOR FURTHER INFORMATION CONTACT: Joseph M. Sheehan, Center for Devices and Radiological Health (HFZ–84), Food and Drug Administration, 2094 Gaither Rd., Rockville, MD 20850, 301–594–4765, Ext. 157.

SUPPLEMENTARY INFORMATION:

I. Background

Blood culturing system devices are diagnostic devices used in clinical settings to detect the presence or growth of bacteria, fungi, or other microorganisms from blood samples or from samples of other body fluids that are normally sterile. The process involves testing for these microorganisms by inoculating the patient's sample directly into broth media or by inoculating a processed sample concentrate onto agar media. Microbial growth is monitored either by traditional manual methods (visual inspection, microscopic evaluation, and/or subculturing) or by instrument-assisted (automated) monitoring of microbial metabolic activities, such as the detection of increased presence of carbon dioxide or changes in fluorescence, bioluminescence, or ATPase activities.

In the **Federal Register** of November 9, 1982 (47 FR 50814 at 50826), FDA classified blood culturing system devices into class I (21 CFR 866.2560). In the **Federal Register** of June 12, 1989 (54 FR 25042 at 25046), FDA published a final rule exempting microbial growth monitors, subject to certain limitations, from the requirement of premarket notification. In the **Federal Register** of April 26, 1991 (56 FR 19333), FDA proposed to revoke this exemption for blood culturing system devices because of safety and effectiveness considerations. FDA determined, on reconsideration, that blood culturing system devices do not meet the criteria for exemption identified in the regulation published in the **Federal Register** of June 12, 1989.

Although current efforts have been directed toward streamlining the regulation of in vitro diagnostic devices, FDA's revocation of the blood culturing system devices exemption is necessary because it is based on significant safety and effectiveness considerations.

Subsequent to June 12, 1989, through the medical/scientific literature, FDA became aware of a significant number of problems related to these devices. These problems include: (1) Failure of media to support growth of certain organisms; (2) false negative and false positive results; and (3) cross contamination of cultures. Also, in the early 1990's, the use of instrument assisted microbial growth monitors, originally intended for blood culturing, started to be commonly used to detect, recover, and provide a complete panel of susceptibility results for *Mycobacterium tuberculosis*.

Since these devices are relied upon for rapid diagnosis of bacterial or fungal infection, and are commonly used to detect, recover, and determine susceptibility of *Mycobacterium tuberculosis*, the reported failure of these devices raises significant questions of safety and effectiveness. Bacterial or fungal infections of the bloodstream may be life-threatening. Tuberculosis is a disease of serious health consequences for the patient and its potential for quick dissemination is a very significant public health concern. Malfunction of these devices, therefore, could result in misdiagnosis and mistreatment, thus endangering patients, health care professionals, and the public at large.

Because of safety and effectiveness concerns presented by the device, FDA believes it is necessary to revoke the exemption from the premarket notification procedures to enable FDA to monitor the introduction into commerce, by manufacturers and importers, of automated blood culturing system devices, and to determine whether the devices are as safe and effective as legally marketed devices. Devices using traditional manual methods employing visual turbidity measurement or direct counts are not affected by this final regulation.

FDA provided interested persons 60 days to submit written comments on the proposal. FDA received two comments. A summary of these comments and FDA's responses follows:

1. One comment requested clarification of the continued exemption for traditional culture media used with manual blood culture methods. The comment suggested that the amended section contain language that makes it clear that traditional manual blood culture bottles in which microbial growth is detected by visual reading and conventional subculturing techniques are not affected by the revocation of the exemption.

FDA agrees with this suggestion. Conventional media dispensed in blood culture bottles (20 to 100 milliliter volume) with limited entry seals that are used only with conventional manual blood culture procedures (visual observation for signs of microbial growth and routine subcultures and/or microscopic screening for presence of bacteria and fungi) are not dependent on instrument-based monitoring for detection of signs of microbial growth. However, media bottles used with the automated system are an integral part of the system; therefore, any new or modified media to be used with an automated blood culturing system are also subject to the revocation.

2. A second comment objected to the continued exemption for blood culture systems not using automated instrumentation.

FDA disagrees with the comment. Current traditional manual blood culturing methods use media formulations and techniques that have been in use for many years. The types of media used are often commercialized for blood culturing by manual procedures developed and controlled by individual laboratories. In contrast, devices or systems that specify incubation and observation procedures based on a combination of different media or for use with a monitoring component (other than visual inspection for evidence of microbial growth and routine subculture to solid media and microscopic examination) are not exempt from premarket notification.

Closed systems that exclude routine microscopic examination and subcultures would also be considered a microbial growth monitor and would be subject to the revocation. Similarly, any media bottle designed to be used with a microbial growth monitor (blood culture instrument or detection mechanism other than direct observation/subculture/microscopic inspection) for detection of microorganisms from patient specimens would be considered a component of the microbial growth monitor and also subject to the revocation.

II. References

The following information has been placed on display in the Dockets management Branch (HFA–350), Food and Drug Administration, rm. 1–24, 12420 Parklawn Dr., Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Aronson, M. D., and D. H. Bor, ''Blood Cultures,'' *Annals of Internal Medicine*, 106:246–253, 1987.

2. Thorpe, T. C., et al., ''BacT/Alert: An Automated Calorimetric Microbial Detection System,'' *Journal of Clinical Microbiology*, 28:1608–1612, 1990.