This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date August 12, 1991

From Associate Director, Immunology, Hematology, and Microbiology - Division of Clinical Laboratory Devices (HFZ-440), Office of Device Evaluation, Center for Devices and Radiological Health

Subject Review Criteria for Blood Culture Systems

To Interested Manufacturers

We have developed a draft document entitled, "Review Criteria for Asssessment of In Vitro Blood Culturing System Diagnostic Devices." Since the document lists items we will be reviewing, it is intended to assist manufacturers in the preparation of marketing submissions for these types of devices.

Since this area of in vitro diagnostics is rapidly expanding in the clinical laboratory, we are soliciting your ideas, recommendations, and comments regarding the attached review criteria. We will appreciate receiving your comments so that we can incorporate as many improvements as possible in a revision.

Please address comments to:

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Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

Date: August 1991
Version: Original

Draft: DCLD Guidance Document Blood Culture Systems

This is a flexible document representing the current major concerns and suggestions regarding in vitro Blood Culturing Systems diagnostic devices. It is based on 1) current basic science, 2) clinical experience and 3) previous submissions by manufacturers to the FDA. As advances are made in science and medicine, these review criteria will be re-evaluated and revised as necessary to accommodate new knowledge.

REVIEW CRITERIA FOR ASSESSMENT OF IN VITRO BLOOD CULTURING SYSTEM DIAGNOSTIC DEVICES

PRODUCT CODE(S): MDB

REGULATION NUMBER: 21 CFR §866.2560

PANEL: 83 Microbiology

CLASS: I

REVIEW REQUIRED: 510(k)

DEFINITION: This generic type device is intended for use in clinical laboratories as an in vitro test for detection of microorganisms from human blood or other normally sterile body fluids.

PURPOSE:

The purpose of this document is to provide guidance on information to present to the Food and Drug Administration (FDA) before a blood culturing device is cleared for marketing. This information enables FDA to make better informed decisions based on a uniform data base.

I. Background

The terms bacteremia, fungemia and septicemia are sometimes interchanged, but these terms do have different meanings. In this document bacteremia is defined as blood containing bacteria or fungi, while sepsis or septicemia is defined as blood containing bacteria or fungi in association with clinical signs of infection such as fever, chills, tachycardia, hypotension, shock or leukocytosis.

According to the National Hospital Discharge Survey, there was a diagnosis of septicemia at discharge from hospital in 2,570,000 cases from 1979 through 1987. During this period, the number of annual cases increased 139%. The increase in septicemia affected all age groups but was greatest in persons 65 years of age and important in the 15-44 year age group. These changes are thought to reflect at least four factors: 1) improved medical technology that may have increased the survival of immunocompromised patients who are at risk for septicemia; 2) the increased use of invasive devices inside and outside the hospital; 3) increased ability to diagnose septicemia; and 4) number of immunocompromised patients who are at increased risk of developing community acquired septicemia. Bacteremia and fungemia are life-threatening infections that require appropriate medical intervention, including administration of antimicrobial therapy. Septicemia is the thirteenth leading cause of death in the United States[1]. Detection of bacteremia or fungemia has great clinical significance especially in 1) establishing the primary diagnosis for certain high risk patient populations; 2) ascertaining or confirming the bacteriologic cause of a focal infection; 3) providing prognostic information and alerting the physician to potential complications of a focal infection (for example, osteomyelitis or meningitis); 4) providing a means to exclude serious illness (in infective endocarditis); and 5) monitoring antimicrobial therapy. A positive result in a blood culture can directly establish the diagnosis (e.g. infective endocarditis). In other instances, when an organism causing an infection is difficult to isolate from the primary site of infection, a positive blood culture provides indirect evidence (e.g. osteomyelitis).

II. Device Description

A. Historical Background.

Since the earliest application when viridans group streptococci were diagnosed as the cause of "malignant endocarditis", blood cultures have been used whenever physicians suspect the presence of clinically significant bacteremia. Although several other in-vitro tests and clinical findings can be used to detect evidence of septicemia, the blood culture remains the "gold standard" test for defining this condition[2].

Blood culture methods have generally involved the use of multipurpose, nutritionally enriched broth or agar media. Blood is either inoculated directly into broth or biphasic media or the blood specimen is pre-processed before media are inoculated. Monitoring of blood cultures traditionally involved visual inspection, Gram stain and blind subculture of broth cultures. Instrument monitoring for CO_2 production by microorganisms in broth cultures by sampling the bottle head space became commercially available prior to 1976. The original approach utilized ^{14}C labeled substrates in the broth media with detection of $^{14}CO_2$ produced by active bacterial metabolism. Since that time, other methods for detection of CO_2 production have been introduced.

B. Principle of the Test.

The devices that are the subject of this guidance document include all growth dependent blood culture media systems, whether 1) monitored by traditional manual or instrument assisted methods; 2) all devices for direct assessment of the presence of organisms in blood utilizing non growth dependent methods; 3) any device that is considered to be an adjunct to enhance the recovery of microorganisms from blood or other body fluids prior to or during culture (examples are resins for the removal of antimicrobials, or devices that lyse blood cells and/or concentrate, such as the Isolator).

C. Specimen Type(s).

Blood or other normally sterile body fluids, except urine, have traditionally been the kinds of specimens that these devices accommodate.

D. Predicate devices.

Aerobic and anaerobic broth blood culture media bottles (Difco, BBL, Becton Dickinson); combination broth, agar systems (Roche Septi-Chek); blood lysis/centrifugation concentrating (Wampole Isolator); CO_2 monitoring systems (radiometric and infra red Bactecs; BacT/Alert Organon); ARD (antibiotic removal device).

III Specific Performance Characteristics

The FDA requires different types and amounts of data and statistical analyses to be included in a manufacturer's application for marketing of in-vitro diagnostic devices. It also varies according to whether the test is quantitative or qualitative. Additional data may be necessary to substantiate certain claims of intended use or clinical significance. If data presented in the submission adequately demonstrate that there is no difference in test results between different sample types (blood, peritoneal dialysate, synovial fluid) using appropriate statistical studies, e.g. McNemar chi-square test, or paired T test, then test performance characteristics may be determined with one specimen of choice. Otherwise, performance characteristics must be demonstrated for all sample types/matrices claimed for use or which demonstrate statistical differences.

Submission of the following data is required to determine comparative safety and efficacy of Blood Culture Systems using culture or non-culture methodology:

A. Analytical/Laboratory/In Vitro Studies.

Specific parameters of importance to the operation of the device should be supported by data determined with the device. It should be demonstrated that the performance of the device is substantially equivalent to a currently used commercial product which serves as the reference method. All protocols for in vitro testing should be clearly stated. Test data should be presented with analyses and conclusions. The data and statistical evaluation including confidence intervals should be sufficient to determine if the device is substantially equivalent and/or comparatively safe and effective for all claimed specimen type(s)/matrices.

The following performance characteristics should be addressed in a submission for devices that detect the presence of microorganisms in blood or other normally sterile body fluids.

1. In-house Studies Background Information

Key issues in the 510(k) review of a blood culturing device are 1) the patient population appropriate for testing; 2) the kinds of organisms recoverable using the device and 3) the technology utilized by the method. The following descriptive information is required to be included in a 510(k) submission to adequately characterize the new in-vitro device. Appropriate literature references that have been subject to peer review and product inserts for predicate device must be included in the submission.

a) Principle of the test

For instrument-assisted systems, provide the following complete and concise information:

1. Principle of the detection methodology
2. Method of detection
3. Determination of cut off values for the threshold of positivity (all media components of the system).
4. Copy of instrument operators manual
5. Computer software documentation (refer to CDRH Draft 2/1/91 "Reviewer Guidance for Computer Controlled Medical Devices").

For non-instrument systems, provide the following information:

1. Principle of the detection methodology
2. Method of detection
3. Criteria for positivity

b) Accuracy/Recovery Studies.

For systems requiring inoculation, incubation and growth[3,4]:

1. The spiking recovery of known concentrations of a variety of organisms in diluent and in blood, inoculated into media intended to support their growth should be determined i.e. CFU/mL <10, <100,<1000 and time to positivity, with and without blood. Organisms should be representative of those for which the medium is intended to support growth.

2. Detection limits should be determined for threshold positivity for representative organisms that can be recovered for each medium type.

3. Determine what the effect is of blood:broth ratio on recovery of organisms. Provide data to substantiate recommended blood:broth ratio.

4. determine the effect of the addition of any supplements for growth of specific organisms from blood or other body fluids. Provide data to substantiate recommended supplements.

5. Provide complete medium formulations for all medium types intended to be used in the system. Provide documentation of the patient populations for which the media has application.

6. Document the ability of the system to recover brucella, mycobacteria, filamentous fungi, mycoplasma and viruses or its inability should be clearly stated in the labeling.

2. Interference Studies.

Provide an explanation for the conditions under which false positive or false negative results may occur. What, if anything, can the user do to avoid obtaining these results?

3. Specimen Collection and Acceptability

a) Provide a summary of all clinical material that is recommended for use in the device i.e. blood, synovial fluid, pleural fluid, peritoneal fluid, cerebral spinal fluid.
b) Provide a summary of all patient populations for which the device has utility i.e. adult, pediatric, immunocompromised, patients on antimicrobial therapy.
c) Recommendations for methods of obtaining clinical material should be stated i.e. syringe and needle, special collection apparatus, vacuum tube.
d) Provide documentation of the volume requirements (minimum, maximun). What effect can be expected if less than minimum or more than maximum volume is added to the bottle?

C. Clinical Studies

Comparison studies provide data on the ability of the system to accurately detect positive and negative blood culture results as compared to another commercial system legally on the market or to a generally accepted reference method.

Data should be presented to demonstrate that the performance of the new system when used qualitatively is substantially equivalent when compared to that of another predicate device already on the market in the United States. A justification for choice of a comparison method including pertinent references and package inserts of the comparative method must be included.

The tests should be performed on a number of positive and negative clinical specimens adequate to establish the relative diagnostic sensitivity and specificity which should be declared in the performance characteristics section of the package insert.

The clinical studies should consist of an evaluation of assay performance. All diagnostic claims and specific parameters of importance to the operation of the device should be proven.

All test protocols for clinical testing should be given. The test protocols should be carried out by at least three independent investigators at separate locations. Test data should be presented with analyses and conclusions. The data and statistical evaluation should be sufficient to determine whether or not the device is substantially equivalent, and comparatively safe and effective to a predicate device.

The reference method may be a commercially available instrument aided system and/or conventional manual methods using commercially available blood culture media. However, if both methods are used, data analysis must be presented seperately.

Parallel studies of large numbers of specimens should be performed at a minimum of three sites, with a minimum of 2000 blood specimens at each site for each bottle/media type.

1. Clinical Protocol

a) The following information should be submitted relative to the testing sites

1. Name of test site
2. Name of principal investigator(s)
3. Provide a clear description of comparison study protocol for each test site. Include the following information:

a) The objectives of the study
b) Numbers of specimens to be analyzed
c) Methodology

1. Collecting blood cultures- who will collect and from what patient population. How will blood be obtained? How much blood will be obtained?
Designate site i.e. peripheral veinpuncture, indwelling arterial or venous catheter.

2. Inoculating bottles- how much blood into each bottle/medium (b/m), order of b/m inoculation, how many bottles per set; if less than minimum volume obtained how will blood be divided. Time of collection. The volume of blood inoculated into reference and test companion b/m must be the same; a blood culture is defined as the volume obtained at a single draw and the total b/m inoculated from that draw. Splitting the study into an aerobic comparison with the reference method and an anaerobic comparison study is acceptable when the volume of blood required for a four bottle draw exceeds 30ml.

3. Acessioning each b/m- the adequacy of fill for each bottle must be determined. Inadequately filled or overfilled bottles must be excluded from the study but should still be processed to maximize recovery of microorganisms from each culture. Provide a description of the accessioning protocol for each site.

4. Examining and testing bottles- provide the schedule for frequency of testing, examining each b/m for the reference and test systems.

5. Processing suspected positive b/m- criteria for a suspected positive b/m in reference and test system. Each positive b/m should be processed independent of other b/m in a set. A negative b/m should not be examined or tested when another b/m in the set is flagged as a suspected positive (except for terminal subcultures as stated below). Bottles should remain in their respective systems until flagged as suspected positives or for the seven day incubation period. B/m flagged as positive by any criteria should be Gram stained and subcultured. Gram-stain negative cultures should be returned to their respective systems and incubated until either growth occurs on the subcultures, B/m are reflagged as suspected positives, or the original 7 day incubation has expired. B/m confirmed as true positives defined as one that, by any criterion, is suspected of containing growing microorganisms and upon Gram stain or subculture is found to contain microorganisms. The definition makes no judgement as to the significance of the isolate (see 7.g). Positives should be processed according to each laboratory's procedures. A false positive b/m is defined as one that is flagged by the system as positive by any criterion in either system and nothing is seen on Gram stain and subculture is negative. The incidence of false positive b/m should be documented. An explanation for the occurance of false positives should be provided.

6. Terminal subcultures-When growth is detected and confirmed in one or more b/m in a set, but the other bottles in that set are not flagged as suspected positives by the end of the 7 day incubation period, "negative" aerobic bottles should be subcultured onto a chocolate agar plate incubated aerobically in CO_2. "Negative" anaerobic bottles will also be subcultured onto a chocolate plate incubated aerobically and onto a blood agar (or other suitable media) and incubated anaerobically. Terminal subcultures from all b/m in a set should be performed on all instrument monitored aerobic bottles and 10% of the anaerobic negative sets.

7. Data collection-The following data should be collected for each culture judged adequate and included in the study:

a) Time and date blood culture was received in the laboratory (time and date obtained should be recorded, if known).

b) The adequacy of fill for each bottle received.

c) How and when growth of the microorganism(s) were detected in each bottle (time to detection given in the nearest hour).

d) Genus and species of all clinically significant microorganism isolated from a given culture.

e) Which bottles were found to be false positive and by what criterion.

f) Which bottles were found to be false negative and by what criterion.

g) Determine whether or not the microorganism(s) are clinically considered to be a contaminant, the cause of a bacteremia or fungemia, or if this can not be ascertained, unknown. The criteria to determine the clinical significance of isolates should be those of Weinstein et al[5], which include i) date of first positive blood culture, ii) body temperature when positive culture was drawn, iii) peripheral leukocyte count and differential, iv) clinical course, v) results of cultures from other body sites, vi) an assessment by primary care physician.

8. Minimum number of positive blood cultures and patient episodes- A minimum of 600 clinical significant positive blood cultures representing a minimum of 370 patient episodes. A patient episode should be defined as a given time period, i.e. 48 h, 3 days, when one or more blood cultures were obtained from the same patient and the same microorganism was isolated from one or more of the bottles in each set (blood culture); separate episodes can occur in the same patient during a different time period when a different organism was isolated.

If the intended use of the device includes body fluids other than blood a minimum of 20 positive patient episodes for each fluid type must be included.

9. Data analysis

Statistical methods for comparing test and reference methods as outlined by Ilstrup[6] , Arkin and Wachel[7]. should be followed. Analysis of methods should be directed at detection of patient episodes and growth and recovery of defined microorganisms in like media[3].

Suggested format for data submission to aid in the review of the submission can be found in the attachments and tables 1-3.

V. Labeling Considerations (CFR 809.10)

Specimen Collection and Handling

a) State the type of specimen to be collected, e.g., whole blood, synovial fluid, pleural fluid.

b) State the conditions for patient preparation, e.g., fasting, timing of collection, intervals of collection, etc.

c) References for appropriate collection procedures, e.g., NCCLS guidelines, textbooks, journals, etc.

d) State the amount of specimen required, both optimum and minimum

e) Identify interfering substances or conditions i.e. antimicrobial therapy

Quality Control

Information provided in a Quality Control section should include the following information:

a) State what specimens or commercially available products should be used for positive and negative quality control, if materials are not provided with the device.

b) Recommendations for frequency of quality control.

c) Directions for interpretation of the results of quality control samples should be provided.

d) The Quality Control section should conclude with a statement similar to the following: "If controls do not behave as expected, results are invalid".

e) Refer to instument procedure manual when appropriate.

V Bibliography.

1. Centers for Disease Control Increase in national hospital discharge survey rates for septicemia-United States, 1979-1987. MMWR. 1990;39:31-34.

2. Aronson MD, Bor DH. Blood cultures. Annals Int Med. 1987;106: 246-253.

3. Bryan CS. Clinical implications of positive blood cultures. Clin Microbiol Rev 1989; 2: 329-353.

4. Washington JA II, Ilstrup DM. Blood cultures: issues and controversies. Rev Infect Dis 1986;8: 792-802.

5. Weinstein MP, Murphy JR, Reller LB, Lichenstein KA. The clinical significance of positive cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 1983; 5: 35-53.

6. Ilstrup DM. Statistical methods employed in the study of blood culture media. In: Washington JA II. ed. The detection of septicemia. West Palm Beach: CRC Press 1978; 31-39.

7. Arkin CF, Wachtel MS. How many patients are necessary to assess test performance? JAMA 1990; 263:275-278.

Table 1 (a-h) [a]

Site _____ *Aerobic/Anaerobic* Cultures

	Test Device		Reference Device	
	#/total bottles	%	#/total bottles	%
Positive	280/2010	13.9	276/2010	13.7
Monomicrobic	250	89.3	248	89.9
Polymicrobic	30	10.7	28	11.1
Negative	1730/2010	86.1	1734/2010	86.3
False positive [b]	44/1730	2.5	80/1734	4.6
False negative [c]	12/1730	0.7	9/1734	0.5

[a] Provide separate table for each test site by aerobic and anaerobic matched culture result and a summary table for all sites by aerobic and anaerobic culture.

[b] Provide definition of false positive criteria for test and reference methods.

[c] Provide definition of false negative criteria for test and reference methods.

Table 2: False Negative Results [a]

Site _____

Aerobic

	Test Device			Reference Device		
	Flag [b]	day	Organism Isolated	Flag	day	Organism Isolated
1	FN	7	*C. albicans*	P	3	*C. albicans*
2	P	4	*C. parapsilosis*	FN	7	*C. parapsilosis*
3	FN	8	*S. epidermidis*	FN	8	*S. epidermidis*
4	N	7	No Growth	FN	7	*S. morbillorum*

Anaerobic

	Test Device			Reference Device		
	Flag	day	Organism Isolated	Flag	day	Organism Isolated
1	FN	2	*Peptostreptococcus sp.*	FN	7	*Peptostreptococcus sp.*
2	P	3	*S. epidermidis*	FN	7	*S. epidermidis*
3	FN	7	No growth	FN	7	*C. perfringens*
4	FN	5	*P. acnes/S. epidermidis*	N	7	No Growth

[a] Organisms isolated upon terminal subculture; results listed are from paired set of aerobic and anaerobic cultures by site and overall.

[b] Define criteria for flags:

FN - False negative is defined as .....

P - Positive is defined as .....

N - Negative is defined as .....

Table 3 a-f

Site/Overall:_____

Organism Recovered by:	BothTest & Reference	Test Only	Reference Only	Statistical Significance *
Aerobic Gram Negative				
Escherichia coli				
Klebsiella pneumoniae				
Enterobacter cloacae				
Enterobacter aerogenes				
Serratia marcescens				
Proteus mirabilis				
Pseudomonas aeruginosa				
Xanthomanas maltophilia				
Acinetobacter spp.				
Neisseria gonorrhoeae				
Haemophilus influenzae				
Aerobic Gram Positive				
Staphylococcus aureus				
Staphylococcus epidermidis				
Staphylococcus haemolyticum				
Micrococcus spp.				
Pediococcus spp.				
Streptococcus pneumoniae				
Group A Streptococcus				
Group B Streptococcus				
Enterococcus faecalis				
Enterococcus faecium				
Streptococcus spp.				
Listeria monocytogenes				
Corynebacterium spp.				
Bacillus spp.				
Anaerobic				
Propionibacterium acnes				
Clostridium perfringens				
Peptostreptococcus spp.				
Bacteroides fragilis				
Bacteroides ovatus				

Table 3 (Cont'd)

Fungi			
Candida albicans			
Candida parapsilosis			
Cryptococcus neoformans			
Histoplasma capsulatum			
Other			
Mycobacterium avium-intracellulare			

This format should be followed for the following data presentation (use headings as highlighted):

a. All **monomicrobic microorganisms isolated from paired aerobic cultures** by site and overall.

b. All **monomicrobic microorganisms isolated from paired anaerobic cultures** by site and overall.

c. **Clinically significant monomicrobic microorganisms isolated from paired aerobic cultures** by site and overall.

d. **Clinically significant monomicrobic microorganisms isolated from paired anaerobic cultures** by site and overall.

e. All **monomicrobic clinically significant patient episodes** by site and overall.

f. All **polymicrobic clinically significant patient episodes** by site and overall.

* Provide significant *P* values; indicate "not significant" (NS). Provide accompanying explanation of statistical method(s) used.