SUBJECT **PRIORITIZATION AND APPROVAL OF THIRD PARTY TEST**

PURPOSE To provide guidelines for the prioritization and approval process that will be used to determine the order in which experimental IA diagnostic tests will be evaluated in contractor replication and comparison studies, and when appropriate, evaluations of potentially interfering conditions .

LEVEL: Principal Investigator/designee
AsTeC Review Committee
Co- Principal Investigator
Sub-Contractor Personnel
Assay Testing Laboratory staff
Biological Specimen Repository Staff
NIAID Project Officer

SUPPLIES/EQUIPMENT Policy and Procedure Manual
Computer
Word Processing Program
Printer

REQUIREMENTS

1. Review Synopsis

   A. The Review Committee will prioritize the studies with approval of the Project Officer and with guidelines developed with the advice of the Scientific Working Group. In general, this will be based on the following factors:

      1. Scientific merits of the assays to be prioritized

      2. The quality of the pre-testing by the test manufacturer

      3. Inventory of adequate number of samples for testing (sample availability may be limited early, however this will be minimized by the availability of specimens in the pre-existing inventory of the contractor and availability of samples from the NIAID IAAM animal models contractor)

   B. Tests chosen for further evaluation will undergo the following steps to determine their likelihood of success as a new diagnostic tool for IA

      1. Replication of the third party/manufacturer's claims

      2. Comparison to predicate devices, and evaluation for interference.

C. The NIAID Project Officer (PO) will receive reports following each stage of evaluation, will participate in reviews of the performance of the experimental test, and make decisions about its further evaluation in development.

2. Prioritization Scoring Overview

A. A scoring system for candidate assays for rapid diagnosis of aspergillosis will be used. Members of the review group will be provided data for the candidate method related to the parameters in the scoring template.

B. Each reviewer will provide a score, using information from existing tests for comparison.

C. The review group will discuss the scores and supporting information to determine if the device may improve upon the existing methods and thus proceed with further evaluation.

D. Improved accuracy may be a reason for further evaluation even if other parameters are inferior to the existing methods. Conversely simplicity may warrant further evaluation even if specificity or sensitivity is inferior to existing methods.

E. Scoring system template results will be based on a scale of 1 to 5, with 1 equivalent to the best score.

F. The calculated scores will be used as a guide to prioritize tests. The lower the score the higher the priority for consideration. For example, a test with a score <35 would be deemed to have excellent potential, a score of 35-70 to be promising, a score of > 70 would be of questionable value and further discussion with the manufacturer would be needed to make a final determination if it should be considered for testing.

3. Proposed Scoring Template

A. Proposed scoring template is shown below:

Parameter [scoring guideline]	Finding	Score
Limit of detection [<1 ng/ml=1, >100 ng/ml=5] **Sensitivity, clinical [>90%=1, <50%=5]** **Specificity, clinical [% negative] >90%=1, <50%=5** **Precision positive control [CV <5%=1, >50%=5]** **Interference [none=1, >3 common conditions=5]** **Cross-reactivity [none=1, >3 common causes=5]** **Sample stability [room temperature=1, frozen within 1 hour=5]** **Sample preparation [none=1, multiple steps=5]** **Equipment requirement [none=1, non-standard expensive item=5]** **Assay complexity [dipstick=1, >5 steps=5][1]** **Time requirement [<30 min=1, overnight=5]** **Training requirement [<2 hr=1, >1 wk=5]** **Cost for kit [<$10/test=1, >$100/test=5]**		
Total score		
Comment **1. Some factors include multiple steps at different temperatures; reagents that have to be combined before use.**		

B. Examples for existing methods for diagnosis of aspergillosis

1. Platelia *Aspergillus* EIA

Parameter: Platelia *Aspergillus* EIA	Finding	Score
Limit of detection [<1 ng/ml=1, >100 ng/ml=5]	**0.5 ng/ml**	**1**
Sensitivity, clinical [>90%=1, <50%=5]	**80%**	**2**
Specificity, clinical [% negative] >90%=1, <50%=5	**90%**	**2**
Precision positive control [CV <5%=1, >50%=5]	**5-10%**	**2**
Interference [none=1, >3 common conditions=5]	**Pip-tazo**	**3**
Cross-reactivity [none=1, >3 common causes=5][1]	**Penicillium**	**2**
Sample stability [room temperature=1, frozen within 1 hour=5]	**48 hr refrig**	**3**
Sample preparation [none=1, multiple steps=5]	**EDTA boil**	**2**
Equipment requirement [none=1, non-standard expensive item=5]	**EIA**	**3**
Assay complexity [dipstick=1, >5 steps=5]		
Time requirement [<30 min=1, overnight=5]	**3 steps**	**3**
Training requirement [<2 hr=1, >1 wk=5]	**3 hr**	**4**
Cost for kit [<$10/test=1, >$100/test=5]	**1 wk**	**2**
	$16 [86 test/$1400]	**2**
Total score:		**31**
1. *Penicillium, Histoplasma capsulatum,* other endemic mycoses		

2. Fungitell Beta-glucan

Parameter: Fungitell Beta-glucan	Finding	Score
Limit of detection [<1 ng/ml=1, >100 ng/ml=5]	60 pg/ml	1
Sensitivity, clinical [>90%=1, <50%=5]	80%	2
Specificity, clinical [% negative] >90%=1, <50%=5	50%	5
Precision positive control [CV <5%=1, >50%=5]	4-24%	3
Interference [none=1, >3 common conditions=5]	Multiple	5
Cross-reactivity [none=1, >3 common causes=5]	Multiple	3
Sample stability [room temperature=1, frozen within 1 hour=5]	48 hr refrig[1]	2
Sample preparation [none=1, multiple steps=5]	KOH	3
Equipment requirement [none=1, non-standard expensive item=5]	EIA kinetic	3
Assay complexity [dipstick=1, >5 steps=5]		
Time requirement [<30 min=1, overnight=5]	3 steps[2]	3
Training requirement [<2 hr=1, >1 wk=5]	3 hr	4
Cost for kit [<$10/test=1, >$100/test=5]	>1 wk	5
	$26[3]	3
	[42 test/$1080]	
Total score		42

Comment:
1. samples must be frozen after 48 hrs of refrigeration
2. triplicate wells, exclude outer rows of plate & center row, glucan free reagents & materials, complex data calculation, easily contaminated by environmental glucans, no control over if referring labs used glucan free supplies
3. wells do not break apart for single tests, not enough reagent even if wells did break apart, so cost more if don't have 21 specimens to test [2 plates at 21 specimens/plate]

3. Quantitative *Aspergillus* PCR

Parameter: *Aspergillus* PCR quantitative	Finding	Score
Limit of detection [<10 copies/ml=1, >10,000 copies/ml=5]		
Sensitivity, clinical [>90%=1, <50%=5]		
Specificity, clinical [% negative] >90%=1, <50%=5		
Precision positive control [CV <10%=1, >50%=5]		
Interference [none=1, >3 common conditions=5]		
Cross-reactivity [none=1, >3 common causes=5]		
Sample stability [room temperature=1, frozen within 1 hour=5]		
Sample preparation [none=1, multiple steps=5]		
Equipment requirement [none=1, non-standard expensive item=5]		
Assay complexity [1 step=1, >5 steps=5][1]		
Time requirement [<30 min=1, overnight=5]		
Training requirement [<2 hr=1, >1 wk=5]		
Cost for kit [<$10/test=1, >$100/test=5]		
Total score		

Comment
1. Appropriate modifications will be made for qualitative assays.
2. There are no standard assays currently available to calculate a mock score for an Aspergillus PCR assay.

4. Third Party Approval Communications and Documentation

   A. Time from completed application review to approval will be no longer than 4 weeks.

   B. Formal prioritization and summary reports will be prepared, approved by the Project Officer and forwarded to the Third Party applicant.

   D. Merits and deficiencies of third party applicants will be contained within the final review report.

   E. All communications with Third Party applicants will be documented and maintained.

ACCEPTABLE ENDPOINTS: N/A

QUALITY CONTROL: N/A

REFERENCES:

ORIGINAL IMPLEMENTATION DATE: _____

APPROVED BY NIH NIAID Project Officer: _____ DATE _____

APPROVED BY PI/designee: _____ DATE _____

APPROVED BY Laboratory Coordinator: _____ DATE _____