

Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis

This draft guidance, once finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Center for Drug Evaluation and Research, Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

1 Drug Development Tool (DDT) Type: Biomarker

2
3 DDT Tracking Number: [DDTBMQ-000001]
4

5 Referenced Biomarker(s): Galactomannan in serum and bronchoalveolar lavage (BAL)
6 fluid.
7

8 Galactomannan is a heat-stable and water soluble cell wall polysaccharide that is released by
9 *Aspergillus* species during fungal growth.
10

11 This guidance describes a qualified context of use for galactomannan detection in serum
12 and/or BAL fluid. The experimental conditions and constraints (below) describe conditions
13 for galactomannan use in the qualified context. Galactomannan use in drug development
14 not conforming to the complete context of use will be considered on a case-by-case basis in
15 regulatory submissions (e.g., investigational new drug application (IND), biologics licensing
16 application (BLA), or new drug application (NDA)); in such cases, additional information
17 relevant to the expanded use may be requested by the Center for Drug Evaluation and
18 Research product review team.
19

20 This guidance applies to research use only in investigational studies of treatments for invasive
21 aspergillosis (IA), and does not change any regulatory status, decisions, or labeling of any test
22 used in medical care of patients.
23

24 Section I: Context of Use (COU)
25

- 26 A. Use Statement: Galactomannan in serum and/or BAL fluid is qualified as a sole**
27 microbiological criterion to classify patients as having probable IA as defined by the
28 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections
29 Cooperative Group and Infectious Diseases Mycoses Study Group (EORTC/MSG) in

Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis

2008,¹ for enrollment in, and analysis of, clinical trials conducted to evaluate the efficacy and safety of drugs for the treatment of IA.

B. Conditions for Qualified Use:

1. **Assay:** A validated assay (see section III), such as the Bio-Rad Platelia *Aspergillus* enzyme immunoassay (EIA), should be used for galactomannan detection as a biomarker.

2. **Patient populations:**

a. The use of galactomannan, as the sole microbiological criterion for diagnosis of IA, is restricted to patients with hematologic malignancies or recipients of hematopoietic stem cell transplant (HSCT) who also have clinical and radiologic features consistent with invasive fungal infection as defined by EORTC/MSG in 2008 (see footnote 1).

b. Subjects enrolled in a treatment trial who satisfy the clinical and radiologic criteria and the following microbiological criteria can be classified as EORTC/MSG category probable IA when using the Bio-Rad Platelia *Aspergillus* EIA:

Serum: A positive result should be based on a cut-off galactomannan index ≥ 0.5 based on testing of two separate serum samples or a single sample with a value of ≥ 1.0 ; and/or

BAL fluid: A positive result should be based on a cut-off galactomannan index ≥ 1.0 based on testing of two aliquots of a single BAL fluid sample.

The quantitative value of the galactomannan index should be documented in the case report forms and included in the electronic datasets.

c. For other assays, appropriate cut-off parameters (for example, values or indices) should be determined and discussed with FDA prior to initiating the clinical trial. The quantitative value of the galactomannan measures should be documented in the case report forms and included in the electronic datasets.

3. **Limitations of use of the galactomannan assay:**

¹ De Pauw B, Walsh TJ, Donnelly JP, et al. Revised Definitions of Invasive Fungal Disease from European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* (2008) 46: 1813-1821.

Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis

69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111

- a. Use of fluids that contain sodium gluconate should be avoided when performing a BAL. The presence of electrolyte solutions containing sodium gluconate, such as PlasmaLyte, may yield false positive results in the galactomannan assay.
- b. Piperacillin/tazobactam may yield false positive assay results. Patients who have recently received or are receiving this antibacterial drug can be enrolled in clinical trials after samples for galactomannan testing are obtained; however, the timing of administration of the antibacterial drugs in relation to sample collection and name of the manufacturer should be recorded so that a sensitivity analysis can be performed.

FDA is aware of studies in progress to evaluate whether newer preparations of piperacillin/tazobactam exhibit cross-reactivity. If these studies do not eliminate concerns of cross-reactivity with piperacillin/tazobactam, then patients enrolled based upon the galactomannan findings as the sole microbiologic criterion after receiving piperacillin/tazobactam should not be considered evaluable in the primary efficacy analyses. Sponsors are advised to discuss this issue with FDA.

- c. The antibacterial drug amoxicillin/clavulanate has been reported to cause false positive results of the galactomannan assay. Patients who recently received or who are receiving this antibacterial drug should not be enrolled into a study based upon positive galactomannan assay results as the sole microbiologic criterion.
- d. Infection with certain other fungal pathogens, such as *Penicillium*, *Paecilomyces*, *Geotrichum*, and *Histoplasma*, may lead to a false positive galactomannan assay result for *Aspergillus* caused by cross-reactivity. Patients known to be infected with these pathogens should not be enrolled, and if enrolled, should be excluded from the analysis of efficacy.

4. Considerations for sample acquisition and documentation:

- a. Investigators should comply with the standard practice of obtaining a fungal smear and culture on all clinically relevant samples. All positive and negative results should be documented on case report forms and included in the datasets. This is especially important for BAL samples so that the presence of *Aspergillus* species or rare fungal pathogens (such as *Penicillium*, *Paecilomyces*, *Geotrichum*, and *Histoplasma*) that may cross-react with the galactomannan assay are documented.

Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis

- 112 b. A BAL fluid sample should be collected as soon as it is feasible because
113 exposure to mold-active antifungal agents may affect the sensitivity of the
114 galactomannan assay.
115

116 **5. Analysis of study results:**
117

- 118 a. When a noninferiority study design is used, the appropriate noninferiority
119 margin should be determined in discussion with FDA at the time the study is
120 proposed within an IND.
121
- 122 b. The primary efficacy analysis should be performed on the modified intent-to-
123 treat population, which is defined as all proven and probable invasive IA.
124 *Proven and probable IA* is defined as per the 2008 EORTC/MSG criteria.
125 However, the use of a positive galactomannan assay (as described above) to
126 classify a patient as probable IA is restricted to patients with hematological
127 malignancies or HSCT recipients.
128
- 129 c. A subset analysis should be done for patients that are diagnosed based on a
130 positive culture and/or histopathology, excluding those whose
131 microbiological diagnosis is based only on a galactomannan positive result.
132
- 133 d. As stated above in section 2.a, patients with hematologic malignancy or
134 recipients of HSCT who have a positive serum galactomannan assay without
135 clinical or radiologic findings consistent with invasive fungal disease should
136 not be enrolled, or if enrolled, should be excluded from analysis of efficacy.
137

138 **Section II: Supportive Information**
139

140 The data to support qualification were obtained with use of the Bio-Rad Platelia *Aspergillus* EIA.
141 The criteria for a positive galactomannan index described here for use in investigational studies
142 of treatments for IA are different from the FDA-cleared Bio-Rad Platelia *Aspergillus* EIA device
143 labeling. The recommendations of this guidance do not alter the labeling recommendations of the
144 galactomannan assay for use in the medical care of patients, and cut-off values specified in the
145 device labeling should continue to be used. The use of different criteria for research is to
146 increase the positive predictive value of the Bio-Rad Platelia *Aspergillus* EIA.
147

148 **Section III: Performance Characteristics of the Assay for the Qualification of**
149 **Galactomannan**
150

151 The data provided to support the current COU relied upon the Bio-Rad Platelia *Aspergillus* EIA
152 for galactomannan detection in serum and BAL fluid that has been cleared by FDA for use in
153 patient care. For performance characteristics of the assay, see the 510(k) summaries on FDA's
154 Web site:

Draft Guidance on Qualification of Biomarker — Galactomannan in studies of treatments of invasive Aspergillosis

155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174

http://www.accessdata.fda.gov/cdrh_docs/pdf2/K023857.pdf (Serum)
http://www.accessdata.fda.gov/cdrh_docs/pdf6/K060641.pdf (Serum)
http://www.accessdata.fda.gov/cdrh_docs/reviews/K093678.pdf (BAL fluid)

A. Other galactomannan assays:

Sponsors using non-FDA-cleared galactomannan assays for studies to be submitted within a drug development regulatory submission to FDA should determine the performance characteristics of the assay using clinical studies to assess performance against defined reference standards and should ensure that the assay is adequate for the COU. For this performance assessment, analytical parameters such as precision, reproducibility, and cross-reaction with non-*Aspergillus* fungal species should be determined. Sponsors should discuss their plans with FDA prior to conducting clinical studies.

For more details, please see supporting information: [Galactomannan Reviews](#)

Instructions for Use in a Regulatory Submission: Please reference DDT # and this guidance in your application.