FDA Experience with Biomarker Qualification:

(Galactomannan for Patient Selection)

Shukal Bala, PhD
Microbiologist/Immunologist
Division of Anti-Infective Products
Office of Antimicrobial Products
CDER, FDA
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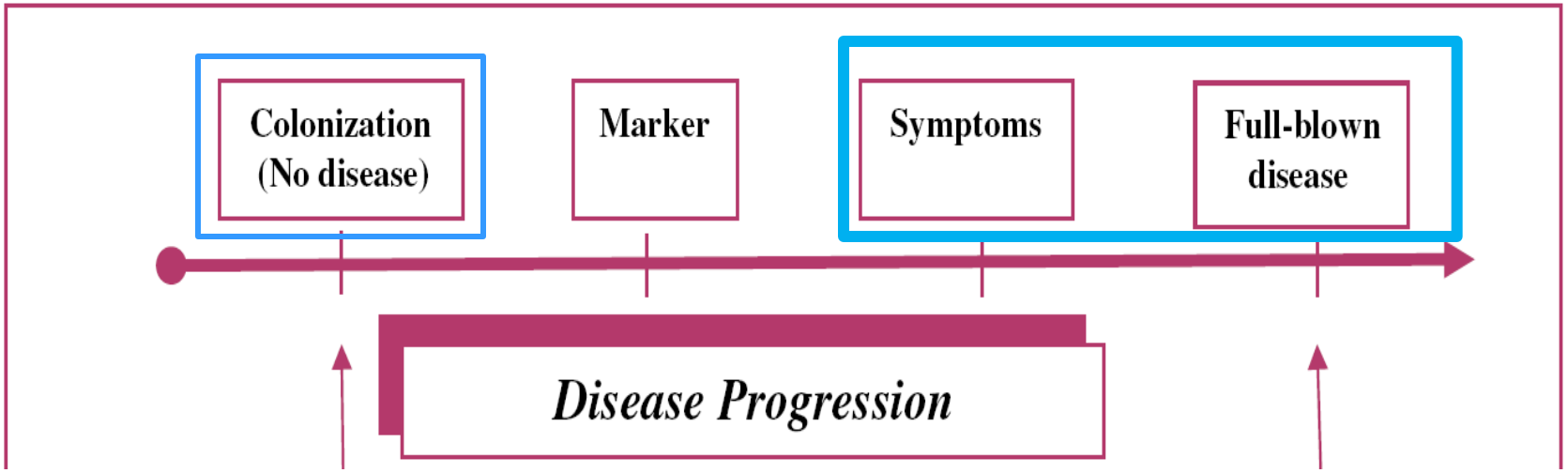
- The opinion expressed in this presentation do not reflect official support or endorsement by the Food and Drug Administration.

- I have no conflict.

Biomarker Qualification
Galactomannan in Invasive Aspergillosis



Asymptomatic

Invasive Aspergillois

Source: Adapted from JR Wingard. New approaches to invasive fungal infections in acute leukemia and hematopoietic stem cell transplant patients. Best Practice and Research Clinical Hematology (2007) 20 (1): 99-107
http://www.sciencedirect.com/science/article/pii/S1521692606000880

Invasive Aspergillosis

- Clinical trials relied on +ve fungal culture patients
  - The sensitivity of culture is low
- Easier, less invasive, biomarker to desired
  - "fit for purpose in Context of Use" to identify patients with IA
- Galactomannan (biomarker)
  - Polysaccharide cell-wall component released by fungal (including *Aspergillus*) hyphae during growth

Invasive Aspergillosis

- FDA cleared test: Platelia *Aspergillus* EIA
  - Indication(s) for use – "…a test which, when used **in conjunction with other diagnostic procedures** such as **microbiological culture, histological examination of biopsy samples** and radiographic evidence, can be used as an aid in the diagnosis of Invasive Aspergillosis."
- If the test is cleared *Aspergillus* test, do we need to go through this biomarker qualification?
  - Yes. The purpose of the qualification process is to determine whether the galactomannan (biomarker) measured by the cleared test is "**appropriate for the context of use/fit for use"**
    - i.e., to serve as a **sole microbiological criterion** (diagnostic biomarker) to diagnose patients as having probable aspergillosis (without culture or histology).

The Process and Steps

Biomarker Qualification Process
for
Galactomannan

Biomarker Qualification (Galactomannan): for Patient Selection

- Submitter: Mycoses Study Group (MSG)/European Organization for Research and Treatment of Cancer (EORTC), Letter of Intent
- Submission: Multiple publications on Platelia *Aspergillus* EIA testing in Invasive Aspergillosis
  - Summary Report
  - Evaluation of the Literature (29 publications using this assay)
  - Individual References
- Proposal (COU): Platelia *Aspergillus* EIA – positive results from Serum or Bronchoalveolar lavage (BAL) fluid to be used as a sole microbiologic criterion in for the diagnosis PROBABLE Invasive Aspergillosis in the context of patients with hematologic malignancies or hematopoietic stem cell transplants and specific CT findings

Biomarker Qualification (Galactomannan): Review

- Review Team: Medical Officers, Microbiologists and Statisticians from
  - CDER:
    - Office of Antimicrobial Products
    - Office of Translational Sciences
  - CDRH
    - Office of In Vitro Diagnostics and Radiological Health
      Division of Microbiology Devices

- Review Process and Goal: Critically review the available data, look for quantitative evidence of correlation between the test and outcome - in the context of use

Galactomannan in Serum

Cut-off*	# Samples	Studies	Sensitivity	Specificity	PPV	NPV
0.5	Single	6	97 (65-100) n=153	88 (61-94) n=961	53 (24-68) n=343	99 (94-100) n=771
	Consecutive	6	93 (83-97) n=116	91 (75-98) n=603	71 (34-90) n=170	98 (96-99) n=559
1.0	Single	8	93 (65-99) n=214	90 (86-96) n=1176	61 (43-79) n=272	98 (92-100) n=1118
	Consecutive	9	88 (57-97) n=177	98 (93-99) n=1465	85 (72-94) n=157	98 (93-99) n=1485
1.5	Single	9	69 (38-80) n=275	95 (92-99) n=1685	55 (45-93) n=232	96 (90-98) n=1728
	Consecutive	9	75 (30-88) n=146	98 (90-99) n=1159	63 (50-90) n=153	94 (88-98) n=1152

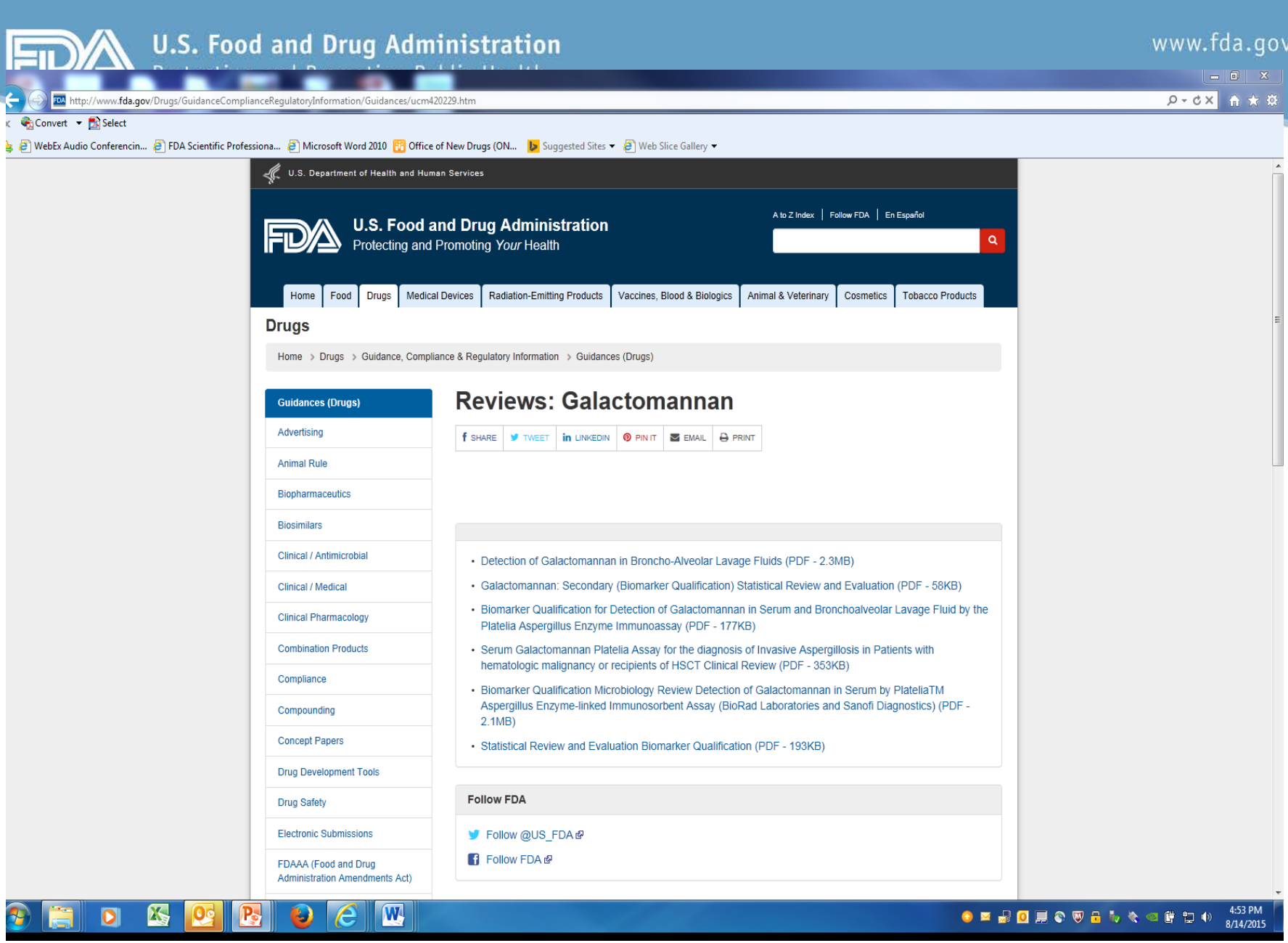
*GM index

Galactomannan in BAL fluid

Reference, Country	Host factor	Total	Proven IPA	Probable IPA	Possible IPA	Without IPA	Estimated Prevalence[b]	BAL GMI ≥ 0.5				BAL GMI ≥ 1.0			
								Sn[c]	Sp	PPV	NPV	Sn[c]	Sp	PPV	NPV
Becker *et al.*, 2003 Netherlands	Hematological malignancies (retrospective)	29	1	6	2	18	28%					100%	100%	100%	100%
	Hematological malignancies (prospective)	53	3	9	12	23	34%					92%	100%	100%	96%
Musher *et al.*, 2004 United States	HSCT	99	49			50		76%	94%			61%	98%		
Verweij *et al.*, 1995 Netherlands	Hematological malignancies	19		7	2	10						71%	90%		
Desai *et al.*, 2009 United States	Hematological malignancies	85	9		37	39	19%	78%	84%			78%	92%	54%	97%
Penack *et al.*, 2008 Belgium	Hematological malignancies	45	17			28	12%					100%	79%	74%	100%
Maertens *et al.*, 2009 Belgium	Hematological malignancies	128	31	27	29	41	45%	97%	80%	68%	98%	91%	88%	76%	96%
Overall Mean (Median)							**23% (23%)**	**83% (78%)**	**86% (84%)**			**85% (91%)**	**92% (92%)**	**81% (76%)**	**98% (97%)**

Galactomannan Biomarker: Draft guidance

I. Context of use (COU)
   A. Use statement
   B. Conditions for qualified use
      1. Assay
      2. Patient population
      3. Limitations of use of the assay
      4. Considerations for sample acquisition and documentation
      5. Analysis of study results
II. Supportive Information
III. Performance Characteristics of the Assay for the Qualification of Galactomannan (with CDRH links)



http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm420229.htm
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf

Summary

The process and components needed to qualify a biomarker using the FDA cleared Platelia assay in the context of diagnosing probable IA for patient selection.

Thank you