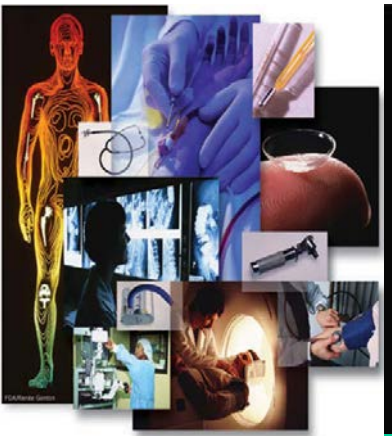

Mock Submissions to FDA/CDRH: History and Lessons Learned

Kyle J. Myers, PhD

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Office of Science and Engineering Laboratories

MDIC CM&S Steering Committee & FDA PI

Center for Devices and Radiological Health

U.S. Food and Drug Administration

June 27, 2014

Outline

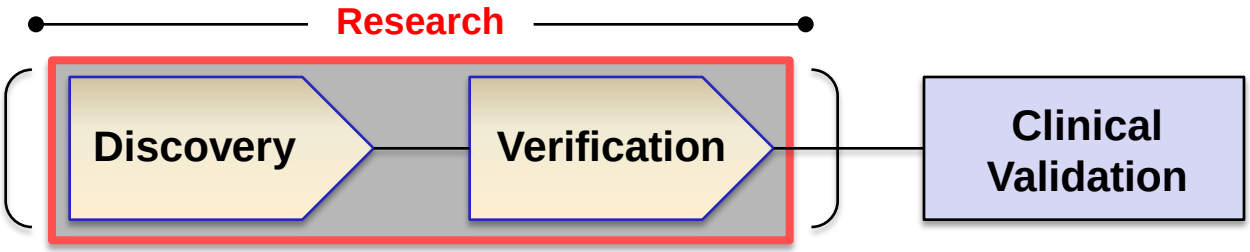
- **What is a Mock Submission**
  - History: Proteomics technologies example
- **Outputs**
- **Why a Mock Submission**
- **Conclusions**

NCI's Clinical Proteomic Technologies for Cancer Initiative (2006-2011)

Assurance At Every Step Of The Biomarker Pipeline

Key accomplishments:

- **Public resources (quality control tools/reference materials with experimental datasets, and well-characterized antibodies)**
- **Analytical reproducibility (Round Robin Studies)**
- **Two-stage standardized workflow**



Clinical Proteomic Technologies for Cancer

Courtesy of H. Rodriguez, NCI

Interagency Oncology Task Force Molecular Diagnostics Subcommittee

Co-Chairs: Henry Rodriguez (NCI), Elizabeth Mansfield (FDA) [Zivana Tezak (FDA)]

Members: Estelle Russek-Cohen (FDA), Gary Kelloff (NCI), James Jacobson (NCI), Larry Kessler (FDA), Mark Raffeld (NCI), Mitch Gail (NCI), Ruth Pfeiffer (NCI), Steve Gutman (FDA), Zivana Tezak (FDA)

"There's really no guidance for multiplex proteomic assays. …. There are unique issues when you start to run a multiple test in a single tube or platform."

Goals	Action Items
Identify analytical validation needs for multiplexed proteomic technologies (e.g., mass spectrometry and affinity-based arrays) in the context of their intended use.	• Convene a meeting/workshop with FDA, NCI, academia, and industry (diagnostics, pharmaceuticals, vendors) to discuss previous and current efforts. • Develop a white paper on multiplexed protein-based clinical assays.

Courtesy of H. Rodriguez, NCI

IOTF MDx Workshop (2008)

- **Primary goal:** Identify key areas to guide translational researchers and developers planning to market diagnostic tests

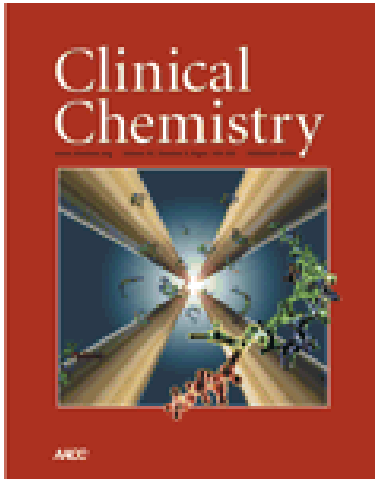
- **Workshop Structure:**
  - FDA: Overview of *In Vitro* Diagnostics
  - Case studies:
    - ***FDA****: MammaPrint and Newborn Metabolite Screening*
    - ***NCI****: MRM-mass spec platforms and Immunological Arrays*

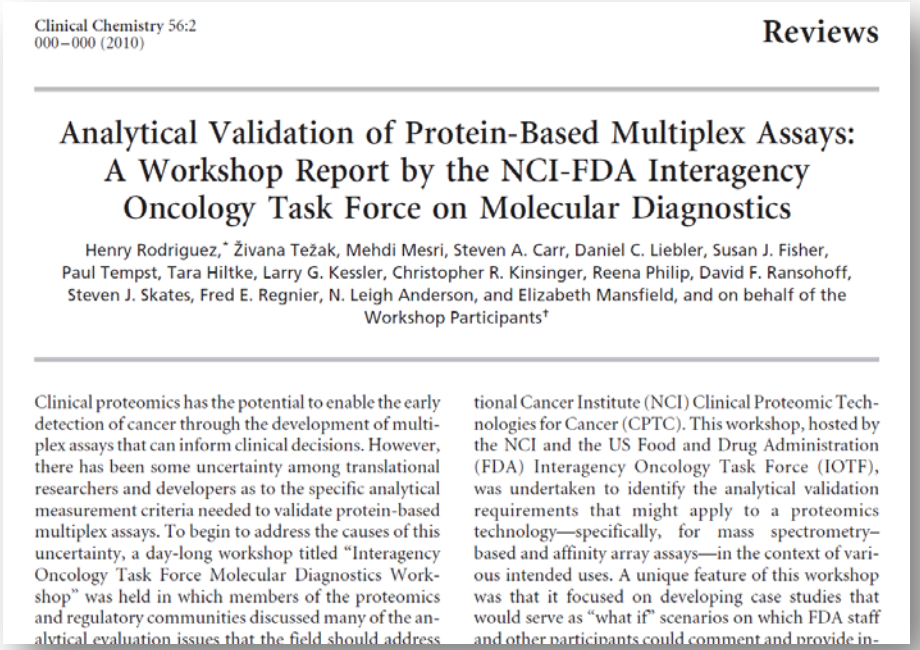
October 30, 2008
Cambridge, MA

Courtesy of H. Rodriguez, NCI

IOTF MDx Workshop Report

- **A workshop report:**
  Analytical validation issues for specific protein-based multiplex platforms (mass spec and affinity-based) to address when seeking FDA approval.





Clinical Chemistry 56:2
000–000 (2010)

Reviews

Analytical Validation of Protein-Based Multiplex Assays: A Workshop Report by the NCI-FDA Interagency Oncology Task Force on Molecular Diagnostics

Henry Rodriguez,* Živana Težak, Mehdi Mesri, Steven A. Carr, Daniel C. Liebler, Susan J. Fisher, Paul Tempst, Tara Hiltke, Larry G. Kessler, Christopher R. Kinsinger, Reena Philip, David F. Ransohoff, Steven J. Skates, Fred E. Regnier, N. Leigh Anderson, and Elizabeth Mansfield, and on behalf of the Workshop Participants†

Clinical proteomics has the potential to enable the early detection of cancer through the development of multiplex assays that can inform clinical decisions. However, there has been some uncertainty among translational researchers and developers as to the specific analytical measurement criteria needed to validate protein-based multiplex assays. To begin to address the causes of this uncertainty, a day-long workshop titled "Interagency Oncology Task Force Molecular Diagnostics Workshop" was held in which members of the proteomics and regulatory communities discussed many of the analytical evaluation issues that the field should address

tional Cancer Institute (NCI) Clinical Proteomic Technologies for Cancer (CPTC). This workshop, hosted by the NCI and the US Food and Drug Administration (FDA) Interagency Oncology Task Force (IOTF), was undertaken to identify the analytical validation requirements that might apply to a proteomics technology—specifically, for mass spectrometry–based and affinity array assays—in the context of various intended uses. A unique feature of this workshop was that it focused on developing case studies that would serve as "what if" scenarios on which FDA staff and other participants could comment and provide in-

Rodriguez H, et al. Analytical Validation of Protein-Based Multiplex Assays: A Workshop Report by the NCI-FDA Interagency Oncology Task Force on Molecular Diagnostics. *Clin Chem*, 56, 237-243, 2010.

Courtesy of H. Rodriguez, NCI

Two Mock Submissions Spawned

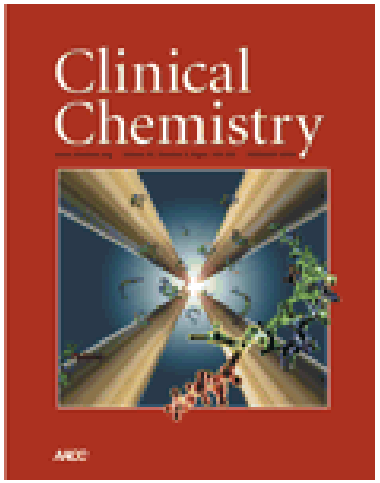
- Multiplex mass spectrometry based assay
  (Immunoaffinity MS protein quantification)
- Multiplex affinity array platform based assay
  (Immunological array for simultaneously assaying multiple glycoprotein isoforms)

Sections submitted

- **Intended Use**
- **Device description**
  - Instrumentation, Reagents
- **Analytical studies**
- **Clinical and statistical evaluation proposal**

Outputs

- **Mock pre-submissions submitted to FDA for review:**
  - Multiplex MRM mass spec platform
  - Multiplex affinity arrays
- **“Lessons learned” intro paper**
  - Served as examples of review comments to the proteomics community




Clinical Chemistry 56:2
000–000 (2010)

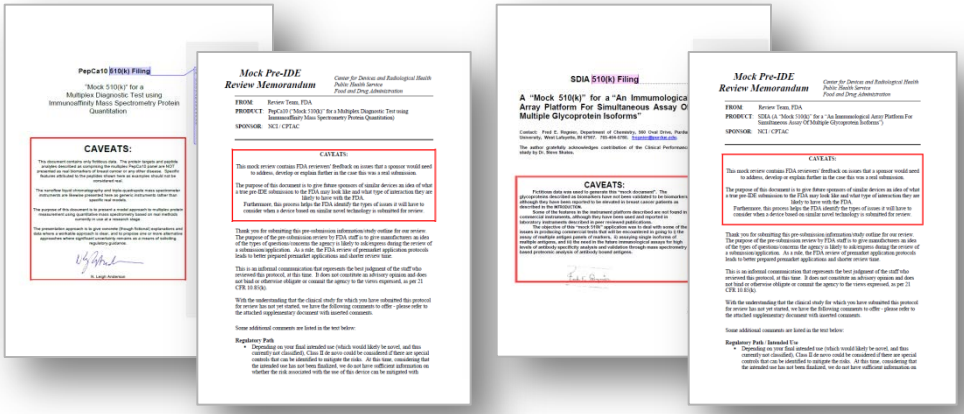
Special Report

Protein-Based Multiplex Assays:
Mock Presubmissions to the US Food and Drug Administration

Fred E. Regnier,[1] Steven J. Skates,[2] Mehdi Mesri,[3] Henry Rodriguez,[3] Živana Težak,[4] Marina V. Kondratovich,[4] Michail A. Alterman,[5] Joshua D. Levin,[4] Donna Roscoe,[4] Eugene Reilly,[4] James Callaghan,[4] Kellie Kelm,[4] David Brown,[6] Reena Philip,[4] Steven A. Carr,[7] Daniel C. Liebler,[8] Susan J. Fisher,[9] Paul Tempst,[10] Tara Hiltke,[3] Larry G. Kessler,[11] Christopher R. Kinsinger,[3] David F. Ransohoff,[12] Elizabeth Mansfield,[4] and N. Leigh Anderson[13*]

Regnier FE, et al. Protein-Based Multiplex Assays: Mock Pre-submissions to the US Food and Drug Administration. *Clin Chem 56*, 165-171, 2010.

Supplementary Materials
(*Multiplex MRM mass spec & immunoaffinity array filing with FDA review memo*)



Courtesy of H. Rodriguez, NCI

IOTF MDx project outcomes

- Mock submissions **published** together with **FDA comments**
- Publications **on the process** provided useful background for proteomic device developers considering FDA submissions

Additional Considerations

- **NCI was the sponsor/submitter**
  - Managed Conflict of Interest concerns
  - Chose submission content
    - Based on what was considered to be most mature
- **Essential to have FDA review division on board**
  - Sees value in devoting resources to mock review

Conclusions

- **Mock Submissions can be means to**
  - Build community (relationships among submitters and FDA)
  - Create transparency
    - ❖ Publication of review comments verbatim
  - Obtain answers to specific questions (beyond what is communicated via FDA guidance)
  - Move the field forward

Acknowledgments

- Presentation materials made available by Zivana Tezak (CDRH/OIVD)
- Some materials adapted from presentations by Henry Rodriguez and Emily Boja (NIH/NCI)
- Background info from Liz Mansfield (CDRH/OIVD)