Mock Submissions to FDA/CDRH: History and Lessons Learned

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• 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)

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

Assurance At Every Step Of The Biomarker Pipeline

Quality Metrics  Greater Confidence  Better Candidates

Research

Clinical Proteomic Technologies for Cancer

Discovery  Verification  Clinical Validation

Courtesy of H. Rodriguez, NCI
**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.”

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


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
• 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


**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 a 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
• 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)