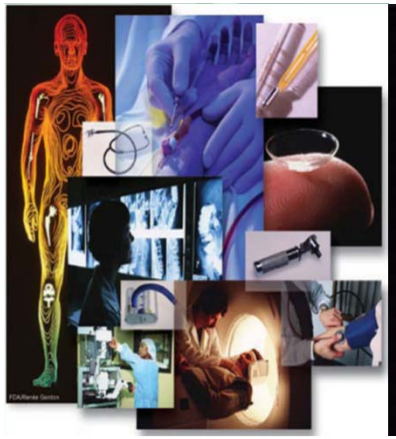


Mock Submissions to FDA/CDRH: History and Lessons Learned

Kyle J. Myers, PhD

Director, Division of Imaging, Diagnostics, and Software Reliability

Office of Science and Engineering Laboratories

Center for Devices and Radiological Health

U.S. Food and Drug Administration

April 12, 2019

Outline

- **What is a Mock Submission**
  - Proteomics technologies example
  - MDIC Virtual patients example
- **Outputs**
- **Lessons learned**
- **Summary**

What is a Mock Submission?

- **Representation of a premarket application**
  - PMA or 510(k) or IDE
  - Hypothetical device with hypothetical characteristics and companion information
  - Collaborative effort involving multiple investigators, companies, stakeholders

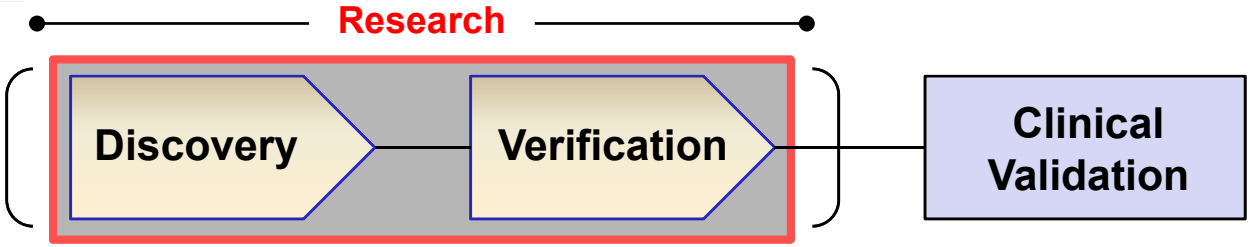
Has CDRH seen mock submissions?

- Yes, in the case of protein-based multiplex assays and virtual patients in a Bayesian trial framework
- Mock submissions provided a mutually beneficial way for FDA and external communities to identify the issues that the field should address to clarify the pathway to market for a new device area

Other information resources

- Discussions with vendors on specific products or submissions
- Info on devices already cleared, approved, granted
- FDA guidances
- Regulations
- Standards
- MDDTs

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



Clinical Proteomic Technologies for Cancer

NCI Initiative was developed to address the pre-analytical and analytical variability issues that were major barriers to the field of proteomics:

(1) Experimental design;
(2) Technological and technical aspects of protein identification;
(3) Variability related to biospecimens collection;
(4) Processes of data acquisition, analysis, and reporting;
(5) Lack of reproducible proteomic technologies; and
(6) Lack of highly characterized and standardized reagents.

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)

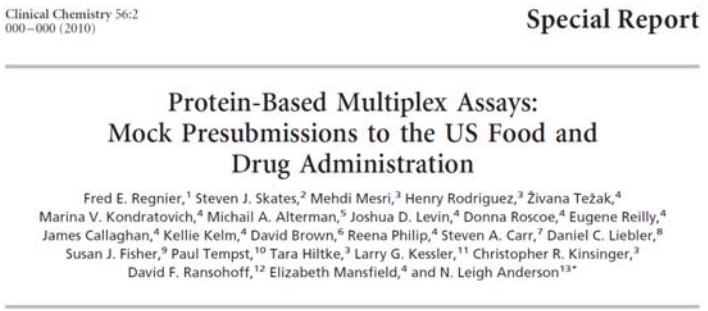
- Multiplex affinity array platform based assay
  (Immunological array for simultaneously assaying multiple glycoprotein isoforms)

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)

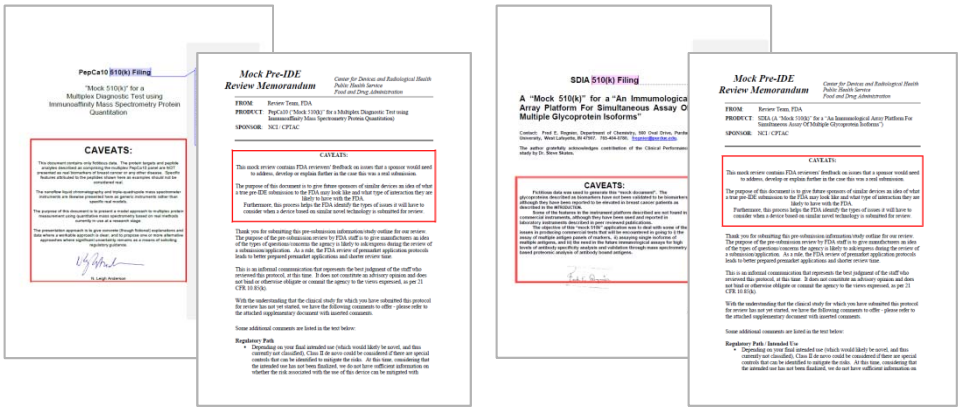
Special Report

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

MDIC Virtual Patient Mock Submission (2015-2017)

- **Proposed pivotal clinical trial for mock device which leveraged simulated clinical performance based on engineering models**

- **Novel methodology using Bayesian methods for incorporating good engineering models**

MDIC computational modeling and simulation working group

- **Going from bench-to-bedside:**
  - Device manufacturers increasingly use engineering models to predict safety and effectiveness outcomes during the product development process
  - Can we leverage simulated clinical performance of a device to improve efficiency of clinical trials?
- Working group brought together scientists from many device companies and FDA under the umbrella of MDIC
  - Collaboration spanned a 2+ year period

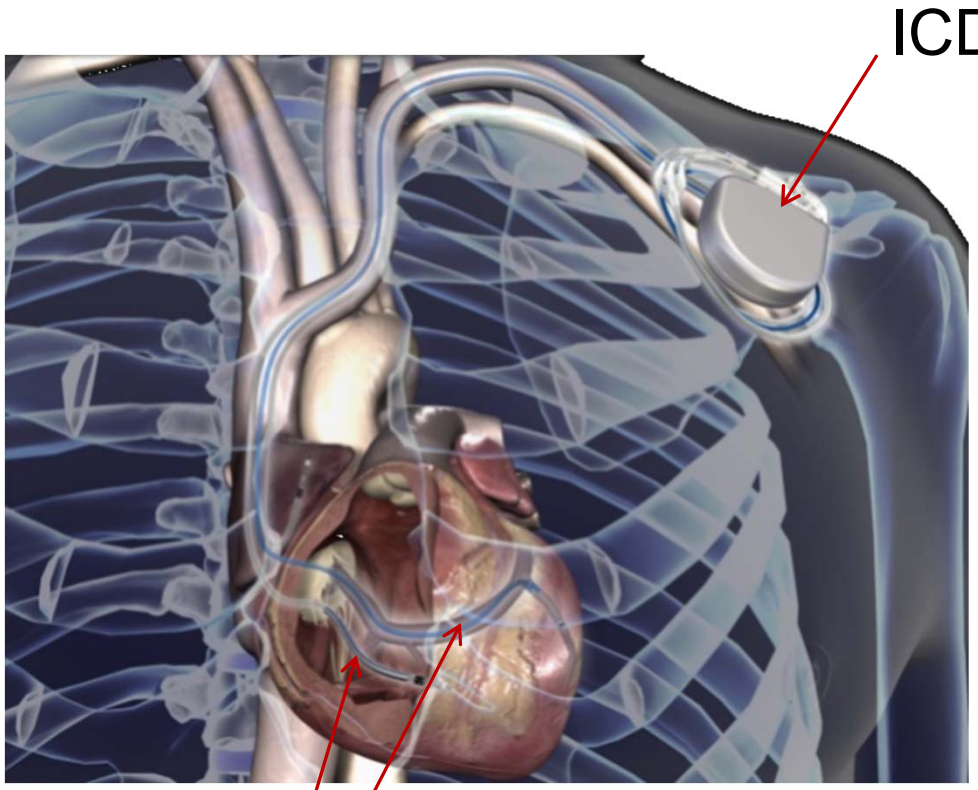
MDIC computational modeling and simulation working group

- Framework for augmenting clinical trial with simulations
  - Utilize engineering models to simulate clinical performance of device in a virtual patient (VP) population
  - Novel Bayesian method combines virtual patients with prospective clinical data from real patients
  - Potentially smaller and more cost-efficient clinical trials

Regulatory feedback obtained via CDRH presubmission (PreSub)

- PreSubs provide regulatory feedback to sponsors prior to an intended submission
  - Submitted detailed clinical trial protocol for a mock device utilizing Bayesian framework for augmenting clinical trial data with virtual patients (VP)
  - Mock submission reviewed by independent team within CDRH comprised of medical officers, engineers and statisticians
- **Multiple rounds of interaction with CDRH reviewers provided timely regulatory feedback**
  - Helped working group to refine methods

Lead Fracture study for mock ICD lead



Lessons learned

- **Challenging to review for regulators**
  - Required collaboration between clinicians, statisticians and engineers at the FDA
  - Multiple face-to-face meetings may be required during review process on account of added complexity
  - Extensive interaction with sponsor needed to identify areas where there are gaps in understanding
- **Mock submission gave FDA reviewers advance opportunity to understand potential regulatory issues related to use of simulations for regulatory approval**
  - Enabled development of regulatory science

Summary

- Mock PreSub and interactions with FDA available online through publications and MDIC website
- Promoted development of industry proposals leveraging these methods
- Fostered a collaborative approach to getting novel products to market through innovative methods
- Benefited the broader ecosystem beyond participants – essential for MDIC 501(3)c status
- Vehicle for creating innovation in regulatory science at reduced investment per sponsor and reduced uncertainty re FDA adoption