FDA Method Development and Regulatory Application in Collaboration with State Partners

The FDA Foods & Veterinary Medicine Research Enterprise

Jeffrey L. Ward DVM, MS, PhD
Senior Science Advisor
FDA Office of Foods and Veterinary Medicine

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Food Safety Modernization Act

FSMA
Risk-informed, Prevention, Public Health Impact

Building Strong Science Infrastructure

Leveraging Resources Establishing Partnerships

Increasing High-risked Compliance

FDA Science Research

FDA Lab Requirements & ISO Standards

State, Federal, International Regulatory Partners

Industry, Domestic/International

FSMA Rules & Requirements

FDA Labs
State, Federal, Foreign Government Labs
Private Labs
How the FVM Science and Research Enterprise Fits In
FVM Science and Research Steering Committee

- A Research and Methods Program to Support the Agency’s Mission and Meet the Needs of its State and Commercial Stakeholders
- Unified Approach: between foods and veterinary medicine program leadership; among researchers; and between researchers and policy makers
- Develop a single Foods and Veterinary Medicine Program (FVM) Science and Research Strategic plan to strengthen core science & research capabilities
- Develop a process for prioritizing FVM Program research
- Develop & implement a unified analytical methods development & validation program aligned with FVM Program priorities
- Improve technology transfer to program offices and field labs
- Establish stakeholder partnerships leverage resources and advance common objectives
Science and Research Steering Committee

- Micro-RCG
- Tox-RCG
- Nano-RCG
- Chem-RCG

- Micro-MVS
- TAGs
- Chem-MVS

- Prioritization Planning
- Method Development Planning
- Method Validation
- Tracking/Resource Management (CARTS)

- Bacterial Recovery & Isolation
- Virus Contamination & Control
- Phenotypic & Genetic Characterization
- Pathogen Detection
- Processing Control & Intervention

- Aquaculture
- Elemental Analysis
- IRCG
- Pesticides
- Persistent Organic Pollutants
FVM’s Broad Laboratory Responsibilities

I. Regulatory Support for Food Safety Programs
   - Outbreak Investigations
   - Surveillance Programs
   - Compliance
   - Domestic and Import Products

II. Research - Basic (foundational) and applied
   - Epidemiology (Traditional and Molecular) and Risk Analytics
   - Bioinformatics, IT infrastructure and Data Sharing Capabilities
   - Methods Development and Validation
     ✓ Emergency needs
     ✓ Emerging concerns (e.g. new threats, changing performance needs)
     ✓ Address current analytical gaps
     ✓ Adapt to innovative technological advances

III. FSMA: Re-set, Partner, Expand, and Integrate
FSMA: Re-set, Partner, Expand, and Integrate

- Ensure alignment with the FVM Strategic Plan & FSMA;
- Risk-informed prioritization
- Coordination and Tracking
- Integration
- Partnerships to expand lab capacity
Annual iterative evaluation of research objectives
- Consistency; Re-evaluation of prior year’s Strategic Outcomes (SOs) as a starting point
- From Strategic Outcomes to Knowledge Gaps to Expected Research Outcomes (EROs)
- Senior leadership responsibilities
  - Identifying the need for new SOs based on events or realized gaps during the current FY
  - Evaluation of current EROs; status and need for carry-over

The research prioritization process
- Assessing the project’s importance and the need for FVM collaboration.
- Prioritization tools — An evaluation/ranking application based on objective metrics, such as:
  - Addresses a Public Health/Animal Health Concern
  - Impact
  - Significant Knowledge Gap/Method Gap
  - Resource Needs and Allocation Concerns
  - Breadth of Applicability
  - Capability to intervene once the research is successful
  - Extent to Which the Research Objective Aligns to the Strategic Outcomes and Knowledge Gaps for More Than One Organization.
  - Research Helps Inform a Risk-based Food Safety System; Supports Preventive Controls
Hazard/Risk-based Strategies
The Future-state Vision

Redefining our approach to developing a strategic program that leads to safer foods by better targeting and more efficient use of laboratory resources through the systematic identification of high risk commodities and an associated hazard i.e. microbial pathogen, chemical analyte, etc. and the analytical tools needed to address the risk.
Risk Ranking

Graphic from HG Claycamp
Risk-Informed Prioritization

Risk management decision-making may consider additional factors.

- Mandates
- Stakeholder Concerns
- Non-Public Health Criteria
- Costs
- Feasibility of Mitigation

Worst risks ➔ Management order ➔
FVM Research Tracking and Assessment Tool

- Component Automated Research Tracking System (CARTS)
  - Research activity descriptions
  - Track progress and manage outcomes
  - Communicates research activities
  - Archival repository – document attachment
  - Reporting, project mining
FVM Research Activities by Center/Office

- CFSAN: 55%
- CVM: 19%
- ORA: 11%
- NCTR: 15%
FVM Research Activities by Discipline

Overview of Intramural Research by Scientific Discipline
* Active CARTS Projects as of February 21, 2014
A Snapshot of the FVM Research Portfolio using CARTS

Tracking capability to assess whether we are directing our research resources where they are needed most.
FVM Research Categories

- Method Development: 46%
- Prevention, Control, and Intervention: 23%
- Molecular Characterization: 3%
- Method Validation: 10%
- Genomics and Proteomics: 8%
- Epidemiologic and Ecological Studies: 3%
- Risk Assessment, Modeling, and Data Management: 7%

FY2014 CFSAN Research By Research Activity
Current FVM Methods Development and Validation Projects

Active CARTS Projects (as of January 12, 2015)

- Total: 129
- Methods Development & Validation: 63
- Methods Development: 66

ORA: 30
CVM: 17
CFSAN: 82

- Microbial & Chemical: 60%
  - Microbial: 56%
  - Chemical: 38%
- General Allergen: 6%
  - Allergen: 5%
  - Chemical: 3%
- Microbial: 30%
FVM Management of Method Development and Validation

Methods Development, Validation, and Implementation Program

Sections included in this document/(Change History)
1. Summary
2. Scope/Policy
3. Responsibilities
4. Procedures
5. Records
6. Supporting documents
7. Attachments
Document history

http://www.fda.gov/ScienceResearch/FieldScience/ucm273423.htm
**Method Validation Process Roles**

**Single-Lab Validated method**

**Methods Validation Subcommittees (CMVS & MMVS)**
- Evaluates MLV plan relative to guidelines
- Oversees MLV or works with TAG
- Evaluates results of MLV
- Confirms validation status of method

**Research Coordination Groups (CRCG & MRCG)**
- Coordinates requests for MLVs with MVS
- Enlists TAG input
- Enlists support for MLV from CFSAN/CVM/ora

**Technical Advisory Groups (TAGs)**
- Advises on relevance of methods (enlists compliance/program)
- Reconciles methods chosen for MLV
- Helps develop MLV plans
- May help coordinate MLV
FDA Method Validation Guidelines

2nd Edition

- Guidelines for the validation of analytical methods for detection of microbial pathogens in foods
- Guidelines for the validation of chemical methods for the FDA foods program

http://www.fda.gov/ScienceResearch/FieldScience/ucm273423.htm
Partnerships to Achieve Our Food Safety Mission

- FSMA Partnerships for laboratory capacity building
- Partnerships to harness technology and develop innovative applications
The Hallmark of the Food Safety Modernization Act (FSMA)

Enhanced Partnerships

Prevention

The Regulatory Lab

Inspections, Compliance, and Response

Import Safety

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov
GENERAL REQUIREMENTS

Performance Standards
- Evaluation of the most significant food-borne contaminants i.e. hazard analyses
- Guidance on action levels
- Consideration of toxicological and epidemiology studies

National Agriculture and Food Defense Strategy
- HHS and DHS coordinated research agenda
- Enhancing preparedness of the agriculture and food system
- Improving agriculture and food system detection capabilities
- Ensuring and efficient response to agriculture and food emergencies

Building Domestic Capacity
- FDA, USDA, and DHS
- Submission of a food safety and food defense research plan
- Identification of food safety programs and practices
- Risk-based activities
- Capacity for laboratory analyses
- Recommendations for surveillance, outbreak response and traceability involving fruits and vegetables
DETECTION AND SURVEILLANCE REQUIREMENTS

- **Laboratory Accreditation**
  - Establish an accreditation program; Criteria for recognition of accreditation bodies
  - Recognition of Laboratory Accreditation

- **Development of Model Laboratory Standards**
  - Appropriate sampling,
  - Analytical testing methodologies
  - Internal quality systems
  - Procedures to handle complaints
  - Qualified lab personnel
  - Any other appropriate criteria established by FDA

- **Testing Procedures**
  - By accredited labs
  - Electronic reporting (a process for potential private lab package reviews by FDA)

- **Integrated Consortium of Laboratory Networks**
  - HHS USDA, DHS, EPA
  - Agreement on common laboratory methods to facilitate the sharing of information
  - Support and integrated response during emergencies

- **Surveillance**
  - Federal, state, local coordination of surveillance systems
  - Hazard/risk-based
  - Strategies to leverage and enhance food safety and food defense capacities, i.e. lab resources, capabilities, epidemiological tools
INTERNATIONAL COLLABORATIONS

- Building Capacity of Foreign Governments with Respect to Food Safety
  - Expand the technical, scientific, and regulatory capacity of foreign countries exporting food to the U.S.
  - Provisions for electronic data sharing, mutual recognition of inspection reports
  - Multilateral acceptance of laboratory methods and detection techniques
FSMA and the Laboratories
Capacity Building through Partnerships

- Regulatory Actions
- Standardized Practices
- Partnerships
- Regulatory Lab Analyses
Success hinges on:

- Mutual Reliance
- Data sharing capabilities
- Acceptance of laboratory data
FSMA, Laboratories, and Partnership Perspectives

I. Provide analytical support

✓ Capacity building; network building
✓ “Burden Sharing - ”hands”, increasing the scope of testing programs
✓ Method Development Research-Incorporation of evolving performance standards/requirements; rapid screening, rapid confirmatory, ID, high-throughput
✓ Risk-informed work-planning and surveillance strategies

II. Establishment of uniform lab-related policies, procedures, standards and programs

✓ Ensuring testing laboratories operate a quality management system; are technically competent, and generate technically valid data; allows laboratories to demonstrate that they produce reliable, high-quality regulated reactions to the FDA
The Integrated Food Safety System (IFSS)

- The Food Safety Modernization Act called for enhanced partnerships and provided a legal mandate for IFSS.
- Governed by the Coordinating Committee (CC), composed of 11 representatives from FDA’s Council of Association President’s and several at-large members from state and local jurisdictions plus federal representatives from FDA, CDC, USDA/FSIS and DHS.

Key elements of the system
- Developing national standards for inspection, laboratory analysis, and sample collection
- Creation of a national work plan to ensure coverage of domestic food facilities
- Developing training and certification programs
- Coordinated emergency response

Currently composed of 10 task groups that have joint federal, state/local leadership
Laboratory Task Group Mission
Develop and Implement national standard laboratory practices and procedures to *promote consistent and meaningful data* among *federal, state, and local laboratory agencies* from environmental and food/feed samples for *compliance and surveillance to support mutual acceptance* of laboratory analytical data.
THE APPROACH; THE STARTING POINT

- Accreditation to ISO 17025 and/or Quality Management Systems
- Develop agreed-upon guidance elements to assess data acceptability; to establish a level of consistency in the laboratory and provide assurance and trust in the quality of data submitted to the end user.

PARTNERS

- The Data Acceptance Work Group:
  - Food and Drug Administration (FDA),
  - Association of Public Health Laboratories (APHL),
  - Association of Food and Drug Officials (AFDO),
  - Association of American Feed Control Officials (AAFCO),
  - Food Safety and Inspection Services (FSIS/USDA)
- The “users” and “end users”
  - Private testing laboratories
  - Federal, state & local regulatory laboratories

LABORATORY WORK STREAM ELEMENTS TO CONSIDER

- It’s not just about how to test
The Accreditation Debate: 
Requirement or Recommendation?

ADVANTAGE OR A BURDEN
- A measure of equivalence, standards of performance
- Costly
- Defining equivalence of accreditation and/or other reliable standards
- Audit stringencies

THE CURRENT PATH FORWARD
- Lab accreditation rule still in formative stage
- FDA ORA/OP program to assist state labs that wish to achieve ISO accreditation
- QMS standards that incorporate the technical and management elements of ISO 17025 at a minimum
All laboratories (accredited or not) should be operating under a Quality Management System (QMS)

- Governs all activities that directly or indirectly contribute to the quality of testing; minimum set of standards;
- May involve additional criteria for food/feed program coordination and alignment

**Pre-analytical**
1. Program requirements
2. Sample collection
3. Chain of custody
4. Sample receipt

**Post-analytical**
1. Reports
2. Record keeping
3. Data Packages
Quality Assurance

SOPs to define the analytical work process

- Sample handling
- Selection of test method
- Equipment calibration, verification, maintenance

Analytical method(s), validation & verification

- Fit for purpose
- Official/reference method verification
- Validation of non-standard methods

Staff training and competency assessment

Proficiency testing

- Proficiency evaluations
- Check sample programs
- “Round robins”

Quality control samples

- Reference materials
- Spikes
- Test results, acceptance criteria, pass/fail

Analytical Worksheets

Full records of the analyses performed

Availability of the raw data

Records, chromatograms, printouts, recorded observations, etc
MDVIP Process

TRANSITION PHASE

- Technology Transfer
- Method Implementation
- Products to Operations

FVM Prioritized Method Needs

Research & Development

Official Methods
FDA Methods Portal

- Compendium of national standard methods and FDA official methods for analysis of human and animal foods
- FDA validated methods
- Selected FERN and Vet-LIRN validated methods
- Publicly accessible – FDA internet website
- Links to the FDA Analytical Manuals (BAM, EAM, PAM, etc.)
### FY16 FVM Method Validation Plan

<table>
<thead>
<tr>
<th>Method</th>
<th>Analyte(s)</th>
<th>Food(s)</th>
<th>Method Application/ Intended use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noroviruses real-time PCR</td>
<td>Noroviruses</td>
<td>Molluscan Shellfish</td>
<td>Sample prep, detection</td>
</tr>
<tr>
<td>Cyclospora conventional PCR</td>
<td><em>Cyclospora cayetanensis</em></td>
<td>Raspberries and Cilantro</td>
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<td>Cyclospora real-time PCR</td>
<td><em>Cyclospora cayetanensis</em></td>
<td>Raspberries and Cilantro</td>
<td>Screening, detection, confirmation</td>
</tr>
<tr>
<td>Salmonella serotyping using multiplex PCR</td>
<td><em>S. enterica</em></td>
<td>Produce, Spices</td>
<td>Detection, molecular serotyping</td>
</tr>
<tr>
<td>Real-time PCR and culture for Non-tuberculosis Mycobacteria</td>
<td>Non-tuberculosis Mycobacteria</td>
<td>Tatoo inks, environmental samples</td>
<td>Detection, confirmation</td>
</tr>
<tr>
<td>Hepatitis A virus real-time PCR for berries</td>
<td>Hepatitis A virus</td>
<td>Berries, frozen</td>
<td>Sample prep, Detection</td>
</tr>
<tr>
<td>Listeria real-time PCR screening</td>
<td>Listeria</td>
<td>Cantalope and soft cheese</td>
<td>Detection, confirmation</td>
</tr>
<tr>
<td>Method</td>
<td>Target</td>
<td>Sample Type</td>
<td>Additional Information</td>
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</tr>
<tr>
<td>PCR-Luminex assay for Salmonella serotyping</td>
<td>Salmonella</td>
<td>Pure culture</td>
<td>Identification, molecular serotyping</td>
</tr>
<tr>
<td>Salmonella Loop-Mediated Isothermal Amplification (LAMP)</td>
<td>Salmonella</td>
<td>Animal feed, pet food, fresh produce</td>
<td>Screening, detection</td>
</tr>
<tr>
<td>Real-time PCR for Salmonella on environmental surfaces</td>
<td>Salmonella</td>
<td>Concrete, stainless Steel and plastic material</td>
<td>Detection</td>
</tr>
<tr>
<td>Real-time PCR for Listeria serotyping</td>
<td><em>L. monocytogenes</em></td>
<td>Celery and soft cheese</td>
<td>Detection, molecular serotyping</td>
</tr>
<tr>
<td>Real-time PCR for Salmonella animal feed-specific serotypes</td>
<td>8 Salmonella serovars</td>
<td>Animal feed</td>
<td>Onsite field screening, Detection</td>
</tr>
<tr>
<td>SeqSero, a web-based application for determination of Salmonella Serotyping using WGS Data</td>
<td>Salmonella WGS data</td>
<td>WGS data</td>
<td>Web-based rapid serotyping tool</td>
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<td>Triphenylmethane dyes in seafood using LC-MS/MS</td>
<td>Triphenylmethane dyes (malachite green, crystal violet, brilliant green, leucomalachite green and leucocrystal violet)</td>
<td>Shrimp, talapia, catfish, and salmon</td>
<td>Regulatory</td>
</tr>
<tr>
<td>EAM 4.7 Inductively Coupled Plasma-Mass Spectrometric Determination of Arsenic, Cadmium, Chromium, Lead, Mercury, and Other Elements in Food Using Microwave Assisted Digestion</td>
<td>As, Cd, Cr, Pb, Hg, Mn, Mo, Ni, Se, Zn</td>
<td>Various</td>
<td>Regulatory, Compliance program</td>
</tr>
<tr>
<td>Determination of FDA Regulated Mycotoxins in Corn, Peanut Butter, and Wheat Flour Using Stable Isotope Dilution and Liquid Chromatography-Tandem Mass Spectrometry</td>
<td>Multi-analyte mycotoxin method (12 mycotoxins)</td>
<td>Corn, peanut butter, and wheat flour</td>
<td>Regulatory, Compliance program</td>
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<tr>
<td>Sterols and Stanols in Foods and Dietary Supplements Containing Added Phytosterols</td>
<td>Phytosterols: total free sterols/stanols and total free steryl/stanol esters: including campesterol, campestanol, stigmasterol, beta-sitosterol, sitostanol</td>
<td>Various foods and dietary supplements</td>
<td>Health claims enforcement</td>
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<tr>
<td>Study Title</td>
<td>Analyte</td>
<td>Food Type</td>
<td>Stakeholder/Regulatory Notes</td>
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<td>Determination of Sulfites in Food Using Liquid Chromatography-Tandem Mass Spectrometry</td>
<td>Sulfite</td>
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<td>Marine Biotoxin Detection: Screening (ELISA) and Confirmatory (LC-MS) Methods for Detecting Neurotoxic Shellfish Poisoning (NSP) Toxins (Brevetoxins) in Molluscan Shellfish</td>
<td>Brevitoxin</td>
<td>Molluscan shellfish</td>
<td>Support stakeholders; possible future use in FDA labs</td>
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<td>Validation of method for detection of genetically engineered salmon</td>
<td>Genetically engineered salmon</td>
<td>Salmon</td>
<td>Stakeholder support</td>
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<td>Quantitation of Chloramphenicol and Nitrofuran Metabolites in Aquaculture Products Using Microwave-Assisted Derivatization, Automated Solid-Phase Extraction and LC-MS/MS</td>
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<td>Analyte extensions of existing pesticide methods</td>
<td>Pesticides</td>
<td>Multiple food products</td>
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<td>Portable Histamine Test Kit</td>
<td>Histamine</td>
<td>Scombrotoxin producing finfish</td>
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<td>Neogen Veratox for Histamine</td>
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Concluding Thoughts: *What Do We Gain?*

- **Lasting success** and impact of FSMA and the FDA’s future vision for an integrated food and feed safety system depends on the strength of partnerships *e.g.* State labs, FERN, VetLIRN.

- **Standardization** of laboratory capabilities and competencies provide confidence of the integrity and scientific validity of laboratory analytical data for acceptance.

- **Analytical support** for an integrated food and feed safety system; mutual reliance; systems recognition that involves partnerships with other federal agencies, with state public health and agricultural agencies, with other public and private stakeholders, and international bodies.

- **Impact**
  - Outbreak investigations,
  - Surveillance activities
    - Import safety strategies
    - Sampling strategies
THANK YOU

Jeffrey.Ward@fda.hhs.gov