Evaluation and Implementation of Rapid Microbiological Methods

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Overview

1. Initial RMM Research
    1. Due diligence activities
2. Developing a Business Case
    1. RMM evaluation
    2. Business case calculations
3. Implementation Process
    1. Risk Assessment
    2. User Requirement Specifications
    3. Validation

Initial RMM Research

- Don’t start with the technologies. Start by evaluating your current testing requirements.
- Take copious and detailed notes during the initial research.

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Initial RMM Research cont.

- Ask yourself some basic questions.
  - What tests are you currently performing?
    - Bioburden
    - Endotoxin
    - Sterility
    - Mycoplasma
    - Custom tests (ELISA, cell based assays)

Initial RMM Research cont.

- Which of your products do you perform the tests on?
  - All products or some of the products
  - Raw materials
  - Environmental samples
- How often do you perform the test?
  - In process
  - Release
  - Consider timeframe (daily, weekly, monthly…)

Initial RMM Research cont.

Example Evaluation Matrix

Test	Product			
	Product 1	Product 2	Product 3	Product 4
Bioburden In process		X(2)	X(26)	X(8)
Bioburden release	X(4)			
Sterility		X(2)	X(26)	X(8)
Endotoxin		X(2)	X(26)	X(8)
ELISA				X(8)

Initial RMM Research cont.

- Evaluate your data
  - Which tests do you perform the most?
    - Tests performed once or twice a year will likely have a lower benefit from an RMM.
    - Higher volume tests typically see bigger benefits.
  - What is the time to result for the high volume tests?
    - Rank the top 3-5 tests based on the time to result. Longest time to result first.

Initial RMM Research cont.

- Evaluate the available technologies
  - Rapid Microbiological Methods website
    - Dr. Miller: www.rapidmicromethods.com
    - Extensive list of currently available methods
    - News and other information regarding RMM
  - Manufacturer's websites
    - Familiarizing yourself with what they have to offer.
      - What the system consists of
      - What the system can do
  - Case studies / White Papers

Initial RMM Research cont.

- Match the RMM to the specific opportunity
  - Quantitative RMM: bioburden, environmental monitoring, endotoxin
  - Qualitative RMM: sterility, mycoplasma and absence/presence assays (USP <62>)
  - Identification RMM: microbial identifications

Due Diligence Activities

- Due diligence activities are performed to protect yourself
- Consider your business requirements
  - What is involved in bringing the system into your company?
    - Vendor audits
    - Implementation timeframe
    - Accounting requirements

Due Diligence Activities cont.

- Consider the regulatory requirements
  - Has this technology been approved for use before?
  - How receptive are the regulators to this technology?
  - Will I have to submit changes to approved products to use this technology?
  - What is needed to validate the system?

Due Diligence Activities cont.

- Obtain some technology training
  - Most vendors will be happy to have you on site to learn about their technology.
  - Most vendors have demonstration labs so you can get some hands on training.
    - How easy is it to learn the process?
      - How many steps? How difficult are they?
      - Is the process clearly defined?
    - Think of potential issues you may have at your facility.
    - How user friendly is the system?

Due Diligence Activities cont.

- Feasibility tests
  - Comparison tests between current method and potential method.
    - See how the results compare.
      - Do both methods give the same result?
      - How is the reporting handled?
      - Does one system give a higher result than the other?
      - What is the quality of the result that is provided.
    - See if the new system can handle your sample.
      - Not all technologies can handle every sample type.

Due Diligence Activities cont.

- Technology: MALDI ID systems
- Feasibility test:
  - 9 isolates: type strains, EM isolates and organisms that are particularly difficult to ID.
  - Identified on MicroSEQ (benchmark)
  - Submitted for MALDI identification
- Evaluation:
  - How many isolates could the MALDI ID?
  - If an ID was generated, how did it compare to the MicroSEQ?

Developing a Business Case

- Costs associated with RMMs can be significant.
  - Feasibility studies, validation activities, capital costs, maintenance
- Cannot make your decision on upfront costs.
  - Long-term costs savings and/or avoidances may make a technology feasible.
- Having a comprehensive business case will help support your decision.

Developing a Business Case cont.

- Determine the overall cost of the conventional method.
  - Direct costs can be directly associated with the method.
    - i.e. consumables, reagents, supplies, analyst labor time, PM/service contracts and calibrations
  - Indirect costs cannot be directly associated with the method.
    - i.e. overhead, hazmat disposal fees, utilities, storage costs

Developing a Business Case cont.

- Determine cost savings/avoidances
  - Reductions in test time / product release cycle
  - Reduction in OOS events / investigations
  - Reduced equipment needs
  - Reduced personnel needs
  - Increases in yield
  - Possibility of lowering inventory holdings

Developing a Business Case cont.

- Determine the overall cost of the RMM.
  - Perform the same evaluation as the conventional method.
  - Capital expenses for the initial investment.
  - Training costs for analysts
  - Qualification and validation costs
  - Regulatory costs (i.e. filing fees, meetings, etc.)

Developing a Business Case cont.

- Return on Investment
  - Ratio of money gained or lost on an investment relative to the amount of money invested.

$$ROI = \frac{\left([\Sigma costs]_{CM} - [\Sigma costs - \Sigma savings]_{RMM}\right)}{RMMinvestment}$$

  - Three outcomes of the calculation:
    - Positive number: investment gain
    - Negative number: investment loss
    - 0: no change

Developing a Business Case cont.

- Payback Period
  - The length of time required to recover the cost of the initial investment.

$$PP = \frac{RMMinvestment}{([\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM})}$$

  - Typically this is determined in years.
  - Ideally a 3 year PP is desired.
  - Depending on methodology and scale of the testing the PP can be longer or shorter.

Developing a Business Case cont.

- Net Present Value
  - Indicator of how much value an investment adds to the company.

$$NPV = \sum_{t=1}^{T} \frac{C_t}{(1+r)^t} - Investment$$

T= total time to consider

r = discount rate (company's investment yield rate)

t = time of cash flow

C_t = cash amount at time t

  - Three outcomes to this calculation
    - < 0: subtracts value from company
    - > 0: adds value to company
    - = 0: no change in company value

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Developing a Business Case cont.

Step	Time	NPV Calculation
1	1 yr.	$PV = \frac{[\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM^1}}{(1+DR)^1}$
	2 yr.	$PV = \frac{[\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM^2}}{(1+DR)^2}$
	3 yr.	$PV = \frac{[\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM^3}}{(1+DR)^3}$
	4 yr.	$PV = \frac{[\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM^4}}{(1+DR)^4}$
	5 yr.	$PV = \frac{[\Sigma Costs]_{CM} - [\Sigma Costs - \Sigma Savings]_{RMM^5}}{(1+DR)^5}$
2	$NPV = (\sum PV_1, PV_2, PV_3, PV_4, PV_5) - RMM \text{ Initial Investment}$	

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Implementation

- Risk Assessment
  - Various methods for risk assessment exist and any one or combination of them can be used.
  - Items to evaluate will vary
    - Failure points with the RMM
    - Products that will be evaluated
    - The types of results the RMM provides
    - How different the RMM is from the current method

Implementation cont.

- Develop the User Requirement Specification
  - This establishes the basic user expectations.
  - Provides documentation of what is required
    - Purpose
    - Technical and functional needs
    - Computer and software requirements
    - Safety requirements
    - Facility requirements
    - Regulatory requirements
    - Supplier requirements

Implementation cont.

- Design Qualification
  - Supplement to the IQ/OQ/PQ
  - Ideally performed prior to purchasing the RMM
  - Document that the intended system design is suitable for the intended purpose.
    - Verifies that all aspects of the URS are met.

Implementation cont.

- Create a Functional Design Specification
  - Details all the functions and requirements that need to be tested
    - Covers all aspects of equipment installation, operation and data handling.
  - The list is crucial to ensure that all items are appropriately tested.
  - All items contained in the FDS must be included in either the IQ, OQ or PQ.

Implementation cont.

- Installation Qualification
  - Establishes that the equipment is received as designed and is appropriately installed.
  - Can be performed by manufacturer or end user.
- Operational Qualification
  - Establishes that the equipment performs all of the desired functions reliably.
  - Can be performed by manufacturer or end user.
- If computers are required for the RMM, ensure they are included in the IQ and OQ.

Implementation cont.

- Performance Qualification
  - Establishes that the equipment performs its intended tasks as defined by the user.
    - PDA Technical Report No. 33 – Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods
    - USP <1223> - Validation of Alternative Microbiological Methods
    - EP 5.1.6 – Alternative Methods for Control of Microbiological Quality

Implementation cont.

Performance Qualification for Quantitative Assays			
	PDA TR#33	USP <1223>	EP 5.1.6
Accuracy	√	√	√
Precision	√	√	√
Specificity	√	√	√
Limit of Detection	√	√	
Limit of Quantification	√	√	√
Linearity		√	√
Range	√	√	√
Ruggedness	√	√	
Robustness	√	√	√
Equivalence	√		√

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Implementation cont.

Performance Qualification for Qualitative Tests			
	PDA TR#33	USP <1223>	EP 5.1.6
Accuracy			√
Precision			√
Specificity	√	√	√
Limit of Detection	√	√	√
Ruggedness	√	√	
Robustness	√	√	√
Equivalence	√		√

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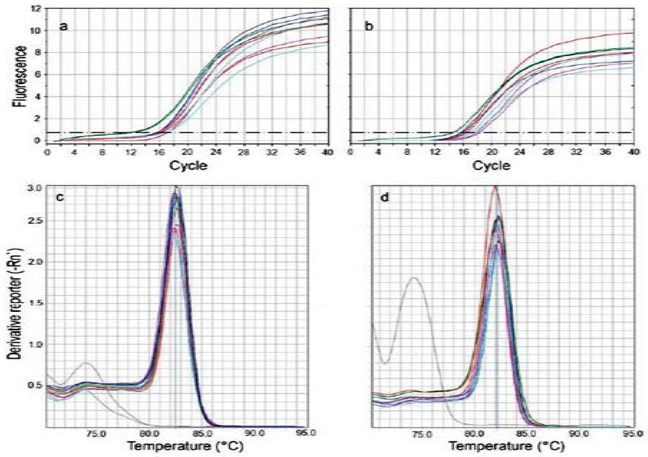
Implementation cont.

Performance Qualification for Identity Tests			
	PDA TR#33	USP <1223>	EP 5.1.6
Accuracy	√		√
Precision	√		√
Robustness			√
Equivalence			√

Implementation cont.



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- Equivalence Studies
  - TR33 and EP 5.1.6 requirement for qualitative and quantitative methods.
  - EP 5.1.6 requirement for ID methods.
  - Demonstrates RMM is equal to or better than current method.

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Implementation cont.

- Equivalence Studies
  - Using standardized microbiological cultures is the initial way to demonstrate this.
  - It also needs to be demonstrated in the intended samples.
    - Can use actual products and/or sample matrices.
    - Perform the studies over a defined number of samples or period of time.
    - Run the RMM in parallel with the current method.
    - To evaluate absence/presence methods spiked samples **must** be included.

Questions???

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