

Rapid Methods: Return on Investments

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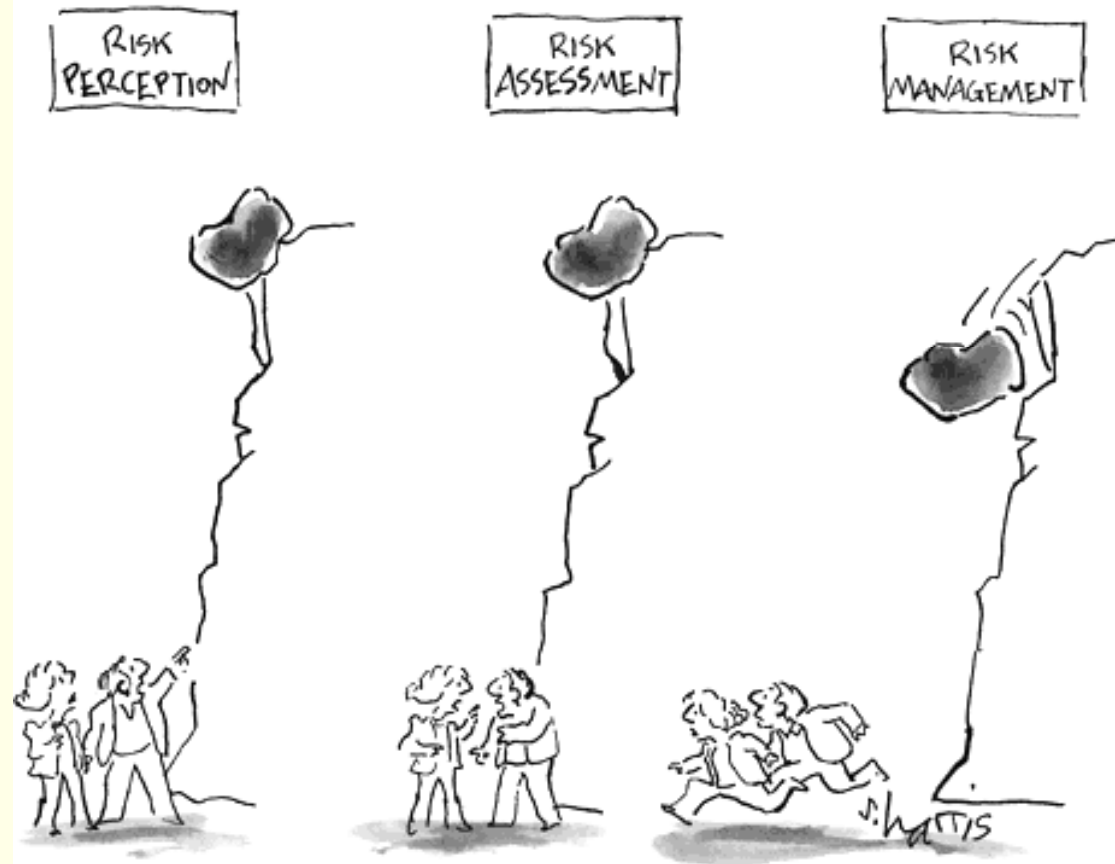
**PDA's 3rd Annual Global Conference on
Pharmaceutical Microbiology**

**Plenary Session 4 – Rapid Methods
Tuesday, October 21, 2008 – 3:15 pm to 5:15 pm**

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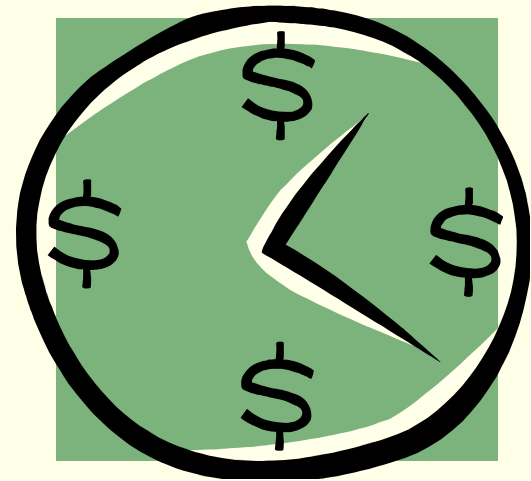


Why the interest in RMMs?



Considerations:

- 1) Evaluate Current/Conventional Methods (CMs)
- 2) Evaluate RMMs
- 3) Calculate the Scientific Benefits of CMs & RMMs as ROI Dollars



Evaluate Limitations of CMs:

- **Time to results is long = days to weeks**
- **Compromise between speed and sensitivity**
- **Results vary with microbial population, media and conditions = unintended selectivity & sensitivity**
- **Spores, stressed organisms require extended periods**

Evaluate Impact of CMs

- **Loss of contaminated products, raw materials**
- **High inventory costs**
- **Increased plant downtime**
- **Increased time to market & reduced shelf life**
- **Decreased capability for new product development**
- **Potential consumer exposure & damage to image**

Evaluate Types of RMMs:

Technology (non exhaustive list)	Detection Sensitivity	Time to result Total Micr. Count
Impedance	10^5-10^6	48-72+hrs
Bioluminescence	10^3-10^4	24-48+hrs
Change with by-products	10^3-10^4	24-48+hrs
Flow Cytometry	10^2-10^3	24+hrs
Autofluorescence	10^2-10^3	24+hrs
Solid-phase Cytometry	1	2-4hrs

Note: See suppliers to get instrument-specific information.

Evaluate RMMs: **Potential Benefits**

- **Reduced warehouse space & costs for raw materials, intermediates and final products**
- **Fast final-product release**
- **Shorter product release cycle times (3 to 6 months of sales)**
- **Time & labor savings in lab, during manufacturing**
- **Reduced number of tests (AET)**
- **Decreased plant downtime**

Evaluate RMMs: **Potential Benefits**

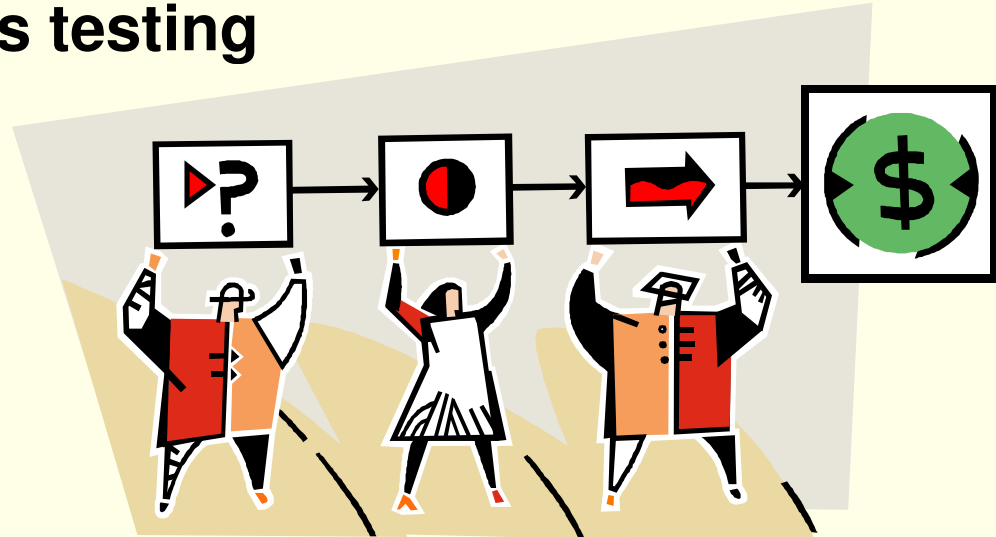
- **Reduced cycle times**
- **Reduction of backorders**
- **Reduction or elimination of product losses**
- **Increased manufacturing capabilities**
- **Risk reduction in manufacturing**
- **Increased business**

Evaluate RMMs: **Potential Benefits**

- **Increased production flexibility**
- **Increased product development capabilities**
- **Robust understanding of manufacturing processes**
- **Proactive control: move from QC to QA procedures**
- **Immediate detection & correction of contamination**
- **Immediate cleaning validation**
- **Better protection of customers & company image**

RMM Applications

- Purified and process water testing
- Raw materials testing
- Fermentation and cell culture monitoring
- Environmental monitoring
- Final products testing



RMM Applications

- **Bioburden testing**
- **Cleaning validation**
- **Antimicrobial effectiveness testing (AET)**
- **Biological indicators**
- **Microbial limits testing of non-sterile drug products**
- **Sterility testing of parenterals and ophthalmics**
- **Immediate investigation**

Supporting Documents

- **FDA - GMPs for the 21st Century**
- **FDA – PAT initiative**
- **PDA – Technical Report #33 (under revision)**
- **USP <1223> Validation of alt. Micro. Methods**
- **EP – Chapter 5.1.6 - Alternative methods for control of microbiological quality**
- **Encyclopedia of RMM**

Calculating **Scientific Benefits** of **RMMs as ROI Dollars**

- Calculate the costs of conventional methods (CM)
- Calculate the costs of implementing RMMs
- Calculate the savings generated by RMMs

Costs of **Conventional Methods**

- **Number of tests per year & price per test**
- **Total testing time (hours) & labor (\$ per hour)**
- **Equipment** (depreciation, calibration, qualification), **lab space**
- **Disposal of used plates**
- **Contamination, biofilm formation, cleaning, etc.**
- **Downtime**
- **Lost opportunities**
- **Estimate total cost over 5 years**

Costs of **RMMs**

- Investment in new equipment
- Number of tests per year (different, fewer)
- Price per test
- Operation time
- Validation documents, packages
- Training
- Maintenance contracts
- Estimate total cost over 5 years

Potential Savings of RMMs

- **Lower inventory costs (space, handling, overhead)**
- **Frees up lab space, need less ancillary equipment**
- **Frees up labor time in the laboratory**
- **Reduced number of tests (AET)**
- **Savings in sanitation measures for water systems**
- **Manufacturing savings (minimizing downtime)**

Potential Savings of RMMs

- **Minimizing contamination costs**
- **Reduced freight costs**
- **Increased business (shorter development time, quicker release of products)**
- **Reduction or elimination of product losses**
- **Increased manufacturing capabilities & flexibility**
- **Risk reduction**

Potential Savings of RMMs

- **Increased product development capabilities**
- **Immediate response to an OOS finding**
- **Immediate cleaning validation**
- **Better protection of company image**
- **Estimate total savings over 5 years**

ROI Formula 1

Return On Investment (ROI)

ROI = Net Benefits / RMM Investment

$$\text{ROI} = \frac{([\sum \text{Costs}]_{\text{CM}} - [\sum \text{Costs} - \sum \text{Savings}]_{\text{RMM}}) \times 5}{\text{Investment}}$$

Σ = Sum of/total

CM = Current or Conventional Method

RMM = Rapid Microbiological Method

Investment = initial investment for the RMM (instrument, any additional pieces of equipment, etc.)

ROI Formula 2

Payback Period (PP)

Payback Period = RMM Investment / Annual Net Benefits

$$\text{PP} = \frac{\text{Investment}}{[\sum \text{Costs}]_{\text{CM}} - [\sum \text{Costs} - \sum \text{Savings}]_{\text{RMM}}}$$

ROI Formula 3

Net Present Value (NPV)

NPV = Cash inflows generated by the RMM investment – RMM Investment (taking inflation and return into account)

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

T = total period of time to consider

t = time of the cash flow

r = discount rate (e.g. company's investment yield rate)

C_t = cash amount at time t

ROI Formula 3 Continued

The period is usually 5 years for RMM investment, thus:

$$\text{NPV} = \begin{aligned} & [\text{Year 1 cash inflow} / (1 + \text{discount rate})^1 \\ & + \text{Year 2 cash inflow} / (1 + \text{discount rate})^2 \\ & + \text{Year 3 cash inflow} / (1 + \text{discount rate})^3 \\ & + \text{Year 4 cash inflow} / (1 + \text{discount rate})^4 \\ & + \text{Year 5 cash inflow} / (1 + \text{discount rate})^5] - \text{Investment} \end{aligned}$$

$$\text{NPV} = \frac{[\sum \text{Costs}]_{\text{CM}} - [\sum \text{Costs} - \sum \text{Savings}]_{\text{RMM}} [\text{year 1 to 5}]}{(1 + \text{discount rate})^{[1 \text{ to } 5]}} - \text{RMM initial Investment}$$

Example: Calculation Model

		Years					
CM:		1	2	3	4	5	Total
	Material Costs	\$	\$	\$	\$	\$	\$
	Labor	\$	\$	\$	\$	\$	\$
	Warehouse Cost	\$\$	\$\$	\$\$	\$\$	\$\$	\$\$
	Other Costs	\$	\$	\$	\$	\$	\$
	Total CM						
RMM:		1	2	3	4	5	Total
	Equipment Cost	\$\$	0	0	0	0	\$\$
	Validation	\$	0	0	0	0	\$
	Service Support	0	\$	\$	\$	\$	\$
	Material Costs	\$	\$	\$	\$	\$	\$
	Labor	\$	\$	\$	\$	\$	\$
	Warehouse Costs	\$	\$	\$	\$	\$	\$
	Other Costs	\$	\$	\$	\$	\$	\$
	Savings	(\$)	(\$)	(\$)	(\$)	(\$)	(\$\$)
	Total RMM						
	ROI: Total CM - RMM	(\$\$)	\$	\$	\$	\$	\$\$

Case Study #1: Major Medical Devices/Pharma Company

Decision Matrix (Technologies evaluated against 11 criteria)

- **Destructive/Non-destructive**
- **Presence/Absence or Enumeration**
- **Cost of Equipment**
- **Cost per Test**
- **Mechanism for Detection**
- **Summary of System**
- **Maximum Volume of Sample**
- **Detection Limit**
- **Throughput**
- **Time to Result**
- **Stage of Development**

Case Study #1: Major Medical Devices/Pharma Company

Decision Matrix Factors – Probability of Success (POS)

- **Four factors rated 1, 3 or 5:
Increasing number = increasing favorability**
 - **Technical challenges**
 - **Regulatory acceptance**
 - **Validation ease**
 - **Uncertainty**

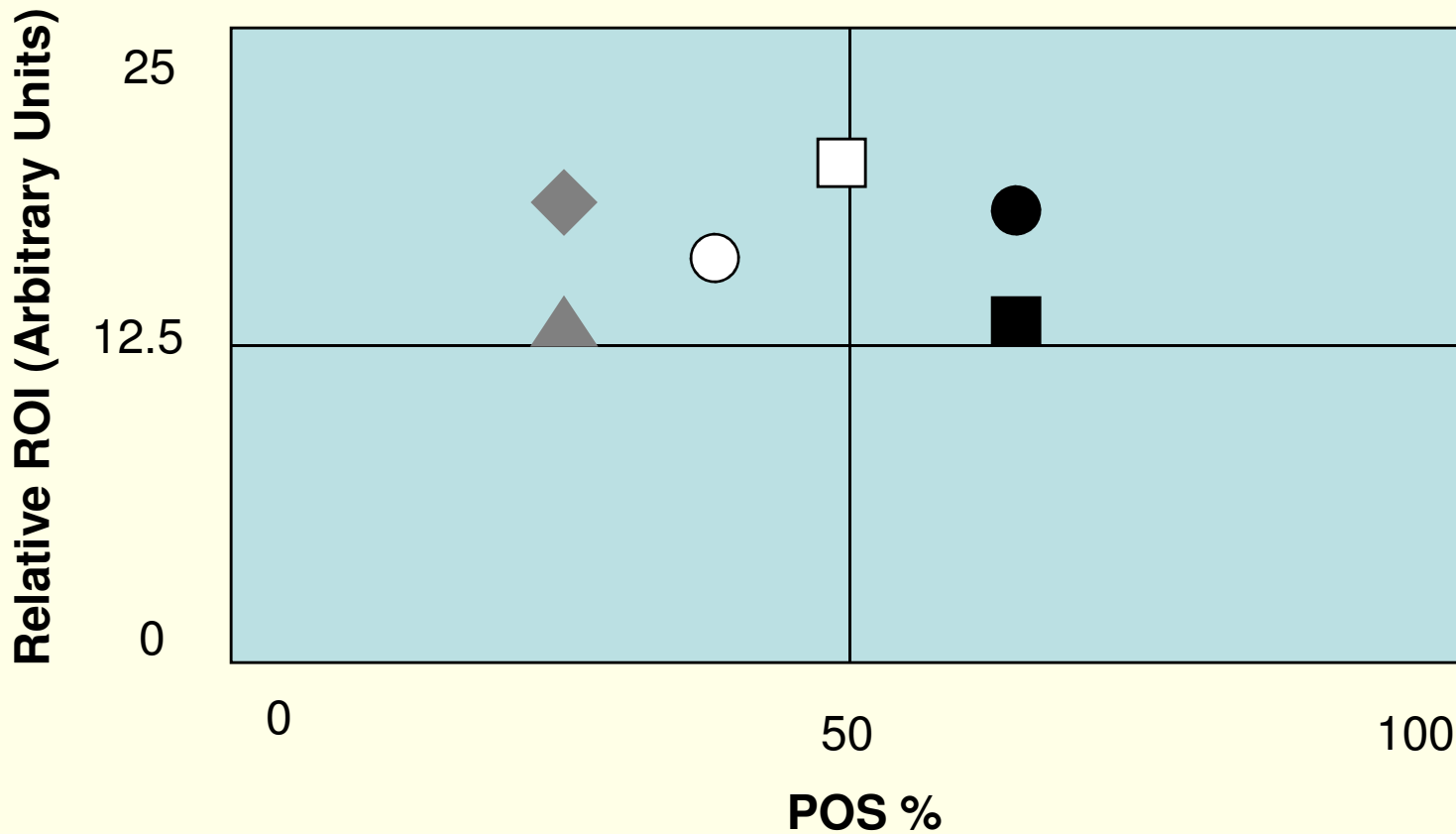
Case Study #1: Major Medical Devices/Pharma Company

Decision Matrix Factors – Return on Investment (ROI)

- **Four factors rated 1, 3 or 5:
Increasing number = increasing favorability**
 - **Capital cost**
 - **Additional manipulation time**
 - **Potential reduced days inventory**
 - **Consumable cost**
 - **Potential loss of batch**

Case Study #1: Major Medical Devices/Pharma Company

Decision Matrix For Candidate Rapid Microbiological Test Replacements For Sterility Test



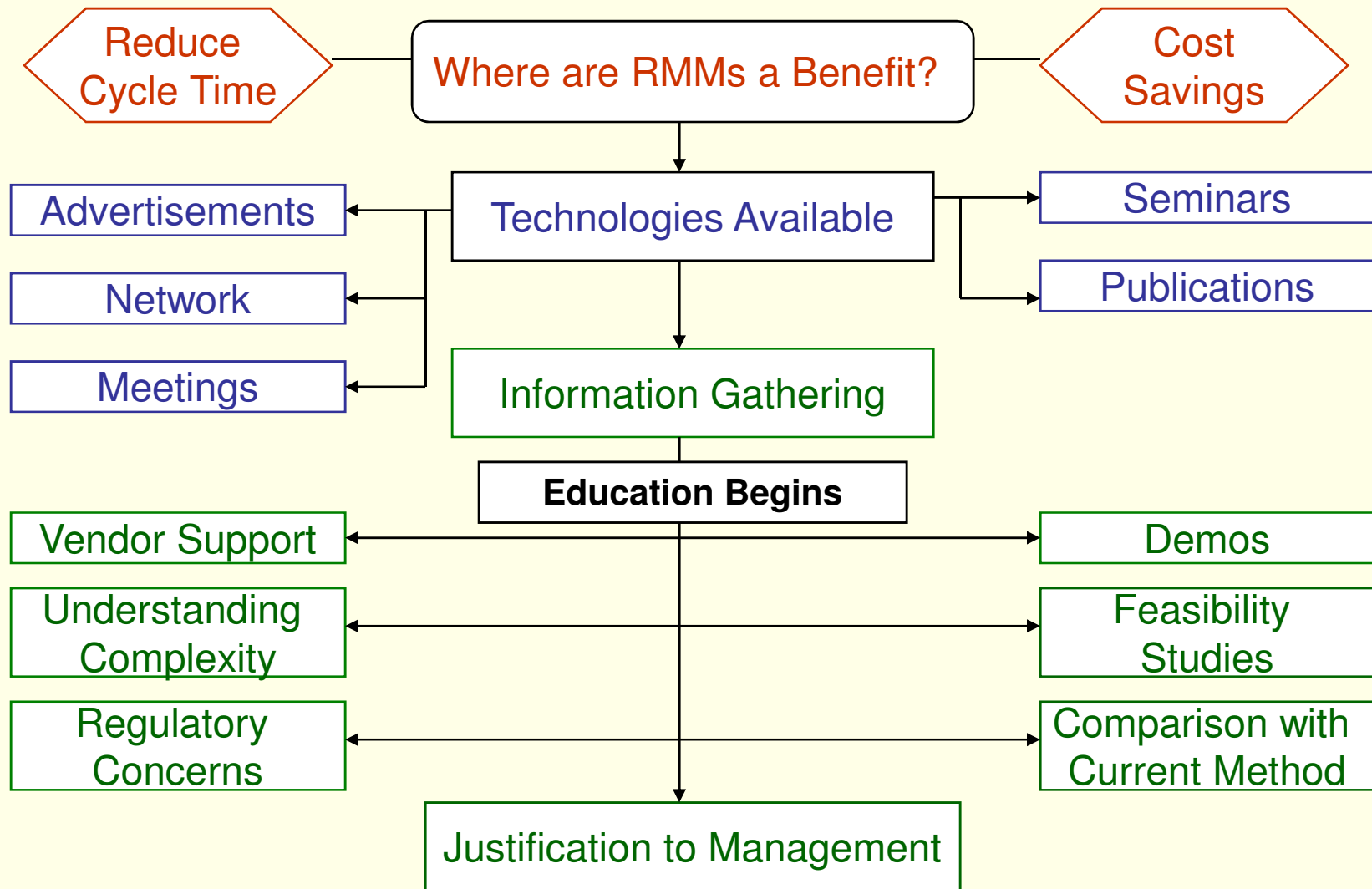
Case Study #2: Major Pharma Co.

Cleaning Validation

- Clean-In-Place Performance Qualifications require bioburden and endotoxin testing of the rinse solution.
- No tanks can be released (tanks are quarantined) until all results are off test and reviewed.
- Growth-based bioburden testing for cleaning validation is a 5-day test (significant loss of production).
- Samples are either rinse water or swabs, both amenable to rapid microbial detection technology.

Case Study #2: Major Pharma Co.

Process for Implementing RMMs

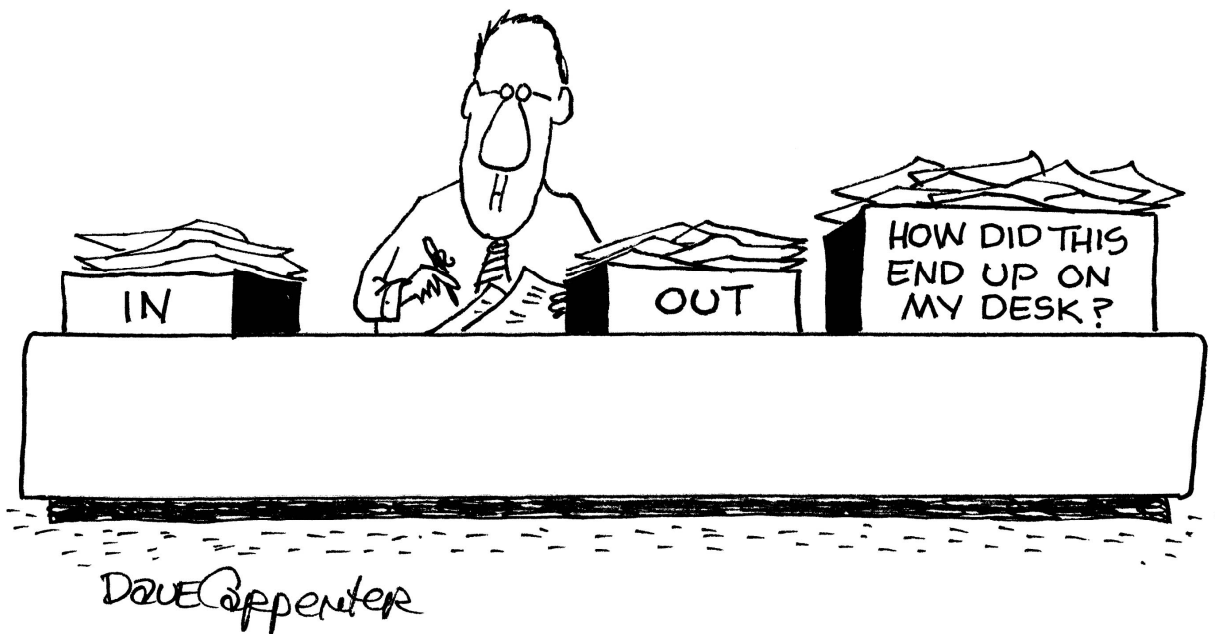


Case Study #3: Med. Devices

	CM: MATERIAL				CM: TIME	RMM	RMM
TEST PHASE	MATERIAL	QTY	UNIT COST	SUB TOTAL	TIME (HRS)	TIME (HRS)	MATERIAL
MATERIAL WASH	BOTTLES(250ML)						
MATERIAL STERILIZATION	MANIFOLD						
	BOTTLES(250ML)						
	TEST TUBES						
	FORCEPS						
	SLEEVES						
	MASK						
	HAIR COVER						
	POUCHES						
	HOOD CLEANNING	HYDROGEN PEROXIDE					
WIPES							
SAMPLE PREPARATION	FLUID-D						
	BOTTLES(250ML)						
	MASK						
	HAIR COVER						
	GLOVES (STERILE)						
	SLEEVES (STERILE)						
	FORCEPS/CUTTERS						
	SYRINGES 10ML						
SHAKER TIME							

TEST PHASE	MATERIAL	QTY	UNIT COST	SUB TOTAL	TIME (HRS)	TIME (HRS)	MATER -IAL
FILTRATION	MANIFOLD (STERILE)						
	FILTERS (STERILE)						
	FORCEPS (STERILE)						
	FLUID-D						
	FILTERS						
	TEST TUBES (STERILE)						
	PIPETTE 10ML						
	PIPETTE1ML						
	TSA						
INCUBATION							
SUBCULTURES	TSA						
INCUBATION							
GRAM STAIN	LOOPS						
	SLIDES						
	SAFRANINE						
	DECOLORIZER						
	CRYSTAL VIOLET						
	IODINE						
	WATER						
	WIPES						
MICROSCOPIC EXAMINATION	BIOBULUS PAPER						
	IMMERSION OIL						
	WIPES						
DOCUMENTATION							
REVIEW							

Why can management be hesitant about rapid methods?



Why Hesitant about RMMs?

- **Budget constraints**
- **Time constraints**
 - **No time to research equipment**
 - **No time to learn new methods, etc.**
- **Technology incompatible with products**

Why Hesitant about RMMs?

- **Fear of validation / regulatory uncertainty / not enough guidance**
- **Fear of false-positives**
- **Fear of higher numbers**
- **Concern about ROI**

Justifying RMMs to Management

5 Considerations to Build Your Business Case

- 1. Evaluate the **Manufacturing Process:**
Risk-based approach**
- 2. List all **RMM benefits** (tangible and intangible)
for **YOUR SITUATION****

Justifying RMMs to Management

3. Justify your **choice of technology**:

- ✓ technology comparative analysis
- ✓ feasibility study
- ✓ reference list
- ✓ validation support (DMF, etc.)
- ✓ technology already validated?
- ✓ scientific papers?
- ✓ 21 CFR Part 11 compliant?

Justifying RMMs to Management

4. **Network & communicate** with Production, Finance, Logistics & Regulatory depts. on ROI calculations
5. Have a clear plan for **validating and immediately implementing RMM in routine use**

Summary

- ✓ **Understand ROI goes beyond the laboratory (manufacturing, warehousing/logistics, etc.).**
- ✓ **Quantify ROI by calculating scientific benefits as ROI dollars.**
- ✓ **Consider intangible benefits (protecting company image, etc.) which are valid in decision making.**

Are You **Ready?**



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Questions? Need More Information?



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