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RAPID MICROBIAL DETECTION

Presented By:

PRESERVATIVE REDUCTION

With Increasing Regulatory Framework

- The main regulatory framework for finished cosmetic products placed on the EU market is Regulation (EC) 1223/2009 on cosmetic products (EU Cosmetics Regulation)
- Governance on substances that may, or may not, be included in cosmetic products.
  - Annex II – Prohibited substances
  - Annex III – Restricted Substances
  - Annex IV – Colorants
  - Annex V – Preservatives
  - Annex VI – UV-Filters

ANNEX V - PRESERVATIVES

Allowable & Unallowable

- Governs the use of list of allowable preservatives in 28 countries.
- By default, this list also indicates which preservatives are not allowed by exclusion
    - Ex: Methylisothiazolinone, commonly used but no longer allowed.
- Governs acceptable use under certain concentrations.
    - Ex: Poly hexamethylene biguinide hydrochloride (PHMB) must now be used at < 0.1%
- While list contains 50+ approved preservatives, few options exist.
    - Preservatives must be compatible with formulation

THE PROBLEM WITH PRESERVATIVES…

Dwindling options

- Preservatives that are not aligned with Annex V must be discontinued or used in reduced concentrations.
- Allowed preservatives are often pH-dependent, temperature sensitive or specific to formula.
  - Sometimes requires re-formulation around the preservative alone.
  - Introduces risk of failure if not properly evaluated for antimicrobial activity, sensitivity, and long-term stability.
- Alternative preservatives do not have the long term data that the old, standby preservatives have.
  - Additional requirements and longer time-to-market to allow for proper risk assessment.

the old methods of dirty manufacturing are

no longer acceptable

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Cosmetic manufacturers must be concerned about
the safety of their ingredients while ensuring
their product is free of contamination.

KEEPING PACE WITH REGULATORY EXPECTATIONS

…and responding to the pressures of business

- Pressure to release product to market as fast as possible, while ensuring the safety of its ingredients and from adulteration.
- Consumer demands are trending toward preservative-free, all natural formulation claims, while they still expect a clean product.
- Regulatory requirements continue to increase, while the amount of allowable preservatives in your product continues to **decrease,** with few new options coming to market.

Production can **no longer** rely on their preservatives to keep their product clean and free of microbial contamination and must adapt or fail in the eyes of regulators and the consumer.

ANTIMICROBIAL ACTIVITY BEGINS IN PRODUCTION

Not with Formulation

- Antimicrobial activity is a primary criteria in selection of a preservative system.
- Microbial contamination is primarily introduced through three main points, both of which are in your manufacturing process:
  - Water used in production.
  - The raw materials and ingredients of your product.
  - Your environment and your personnel.
- These initial sources of contamination, lead to continual sources of contamination in your equipment.

Is unknown or uncontrolled microbial contamination during production making you

preservative-dependent?

Why not **control your process** instead?

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ACHIEVING A STATE OF CLEAN-BY-DESIGN

Reducing Risk by Proactive Quality

- Manufacturers need to adapt to increased regulatory demand and consumer expectations by adopting cGMP (current Good Manufacturing Practices) standards for their production process.
- cGMP's involve consistent, well-documented, and proven practices for inspection of:
  - Environmental sampling of equipment, personnel, and manufacturing areas.
  - Microbial testing of water, raw materials, and finished products.
  - Secure, complete, and appropriate documentation of results and records.

ADDITIONAL GUIDANCE

- Guidance can be found in:
  - ISO 22716:2007 - Cosmetics - Guidelines on Good Manufacturing Practices
  - FDA Guidance For Industry - Cosmetic Good Manufacturing Practices

Raw materials, in-process samples, and final product testing should be implemented as part of a

good manufacturing process

addressing contamination earlier and

faster.

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ALTERNATIVE MICROBIAL DETECTION METHODS

- Rapid microbial detection technology allows companies to quickly and accurately determine whether a product is contaminated, identify the exact organism, and confirm the quality of the product.

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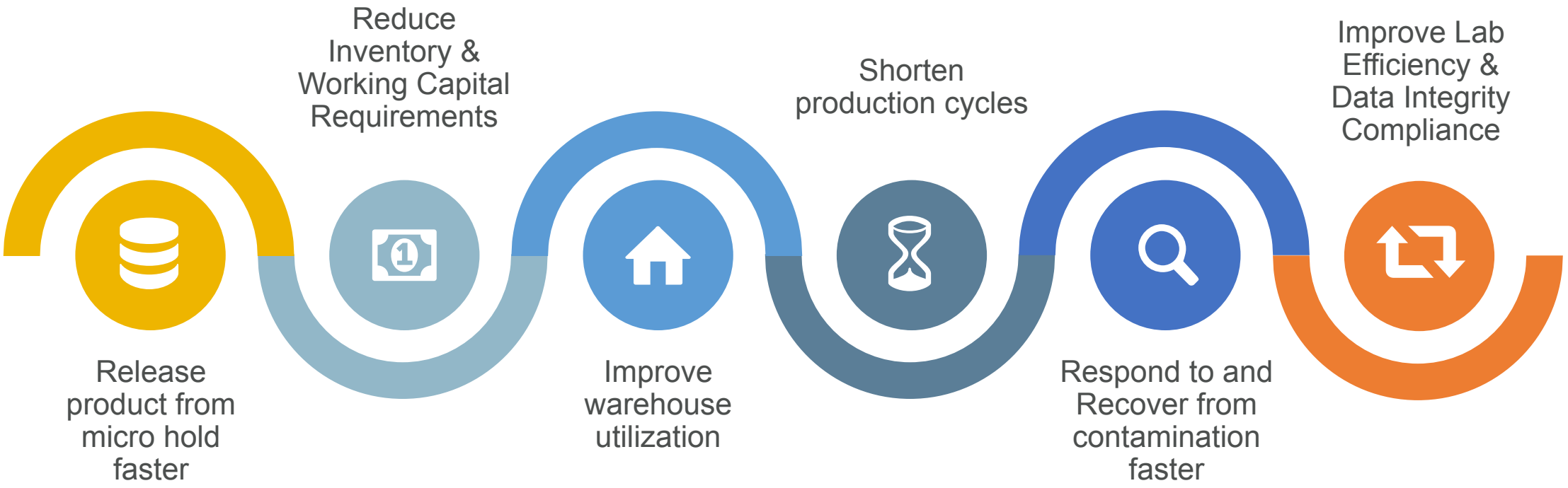
Just being rapid isn’t enough. Your RMM needs to be the

Right Microbial Method

Choosing a rapid method takes more time, energy, and money than ever before. And that’s even before you consider what you’ll need to implement it and ensure it works with your products and methods.

IMPACT OF CELSIS® RAPID MICROBIAL METHODS



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Rapid Microbial Detection Instruments

BUILT FOR SIMPLICITY

Celsis® Rapid Microbial Detection Instruments

Easy integration

Into your current test protocols.
Use your validated method.
Eliminate days of incubation.

Microbial Limits results in 24 hours.

Objective results

replace manual eye counts or visual turbidity checks with automated, instrument based analysis.

Because finding nothing ultimately means everything.

Secure data integrity

and control through on-board, regulatory compliant software. Automated reporting. Multiuser management.

Let your data work for you, instead of against you.

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SAME FEATURES. DIFFERENT SIZES.

Celsis® Rapid Microbial Detection Instruments

the Celsis Advance II™

High capacity. High efficiency.

Up to 120 Assays per Hour

Provides the critical results necessary for critical decisions. Shorten production cycles. Detect contamination events sooner and respond even faster.

the Celsis Accel®

Everything you need. Nothing you don't.

Up to 30 Assays per Hour

Provides the same high-performance detection and reagent compatibility as the Advance II for labs with workloads that are smaller, but no less important.

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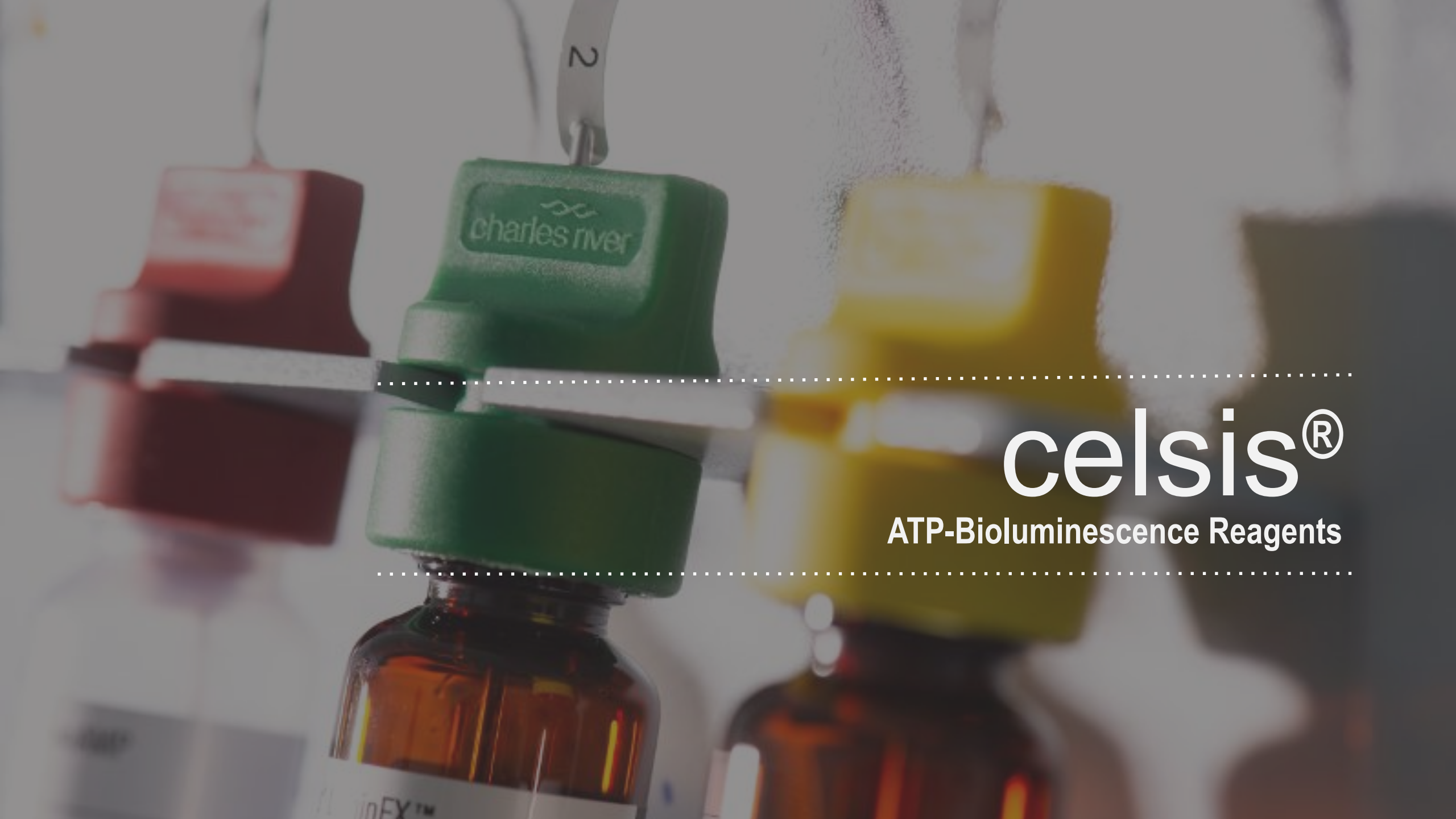

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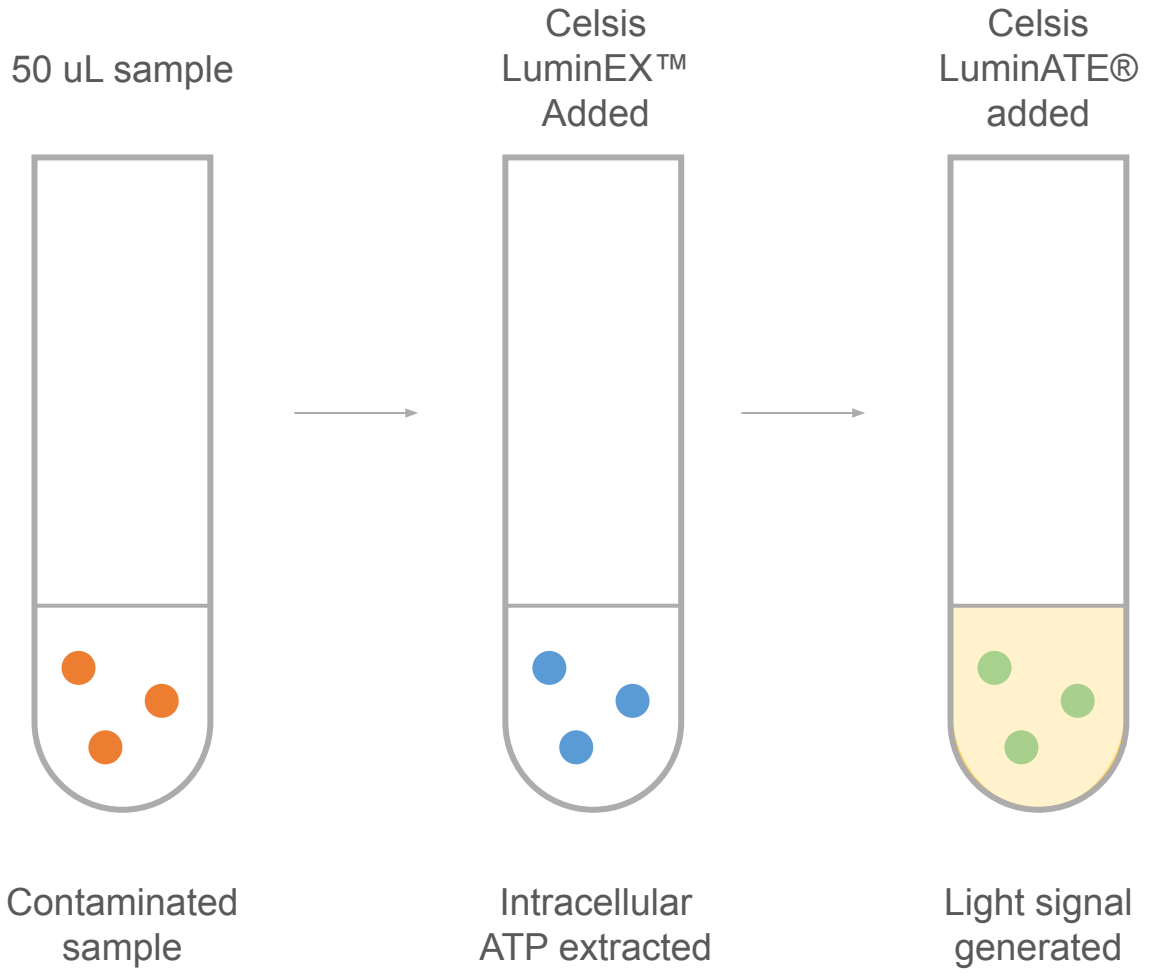
ATP-Bioluminescence Reagents

CELSIS LUMISCREEN™
STANDARD ATP BIOLUMINESCENCE

Celsis® ATP-Bioluminescence Reagents

- Adenosine triphosphate (ATP) is present in all living cells, including bacteria, yeasts, and fungi.
- Standard ATP assays use enzyme luciferase to catalyse microbial ATP and produce light
- Light generated is measured using a luminometer.

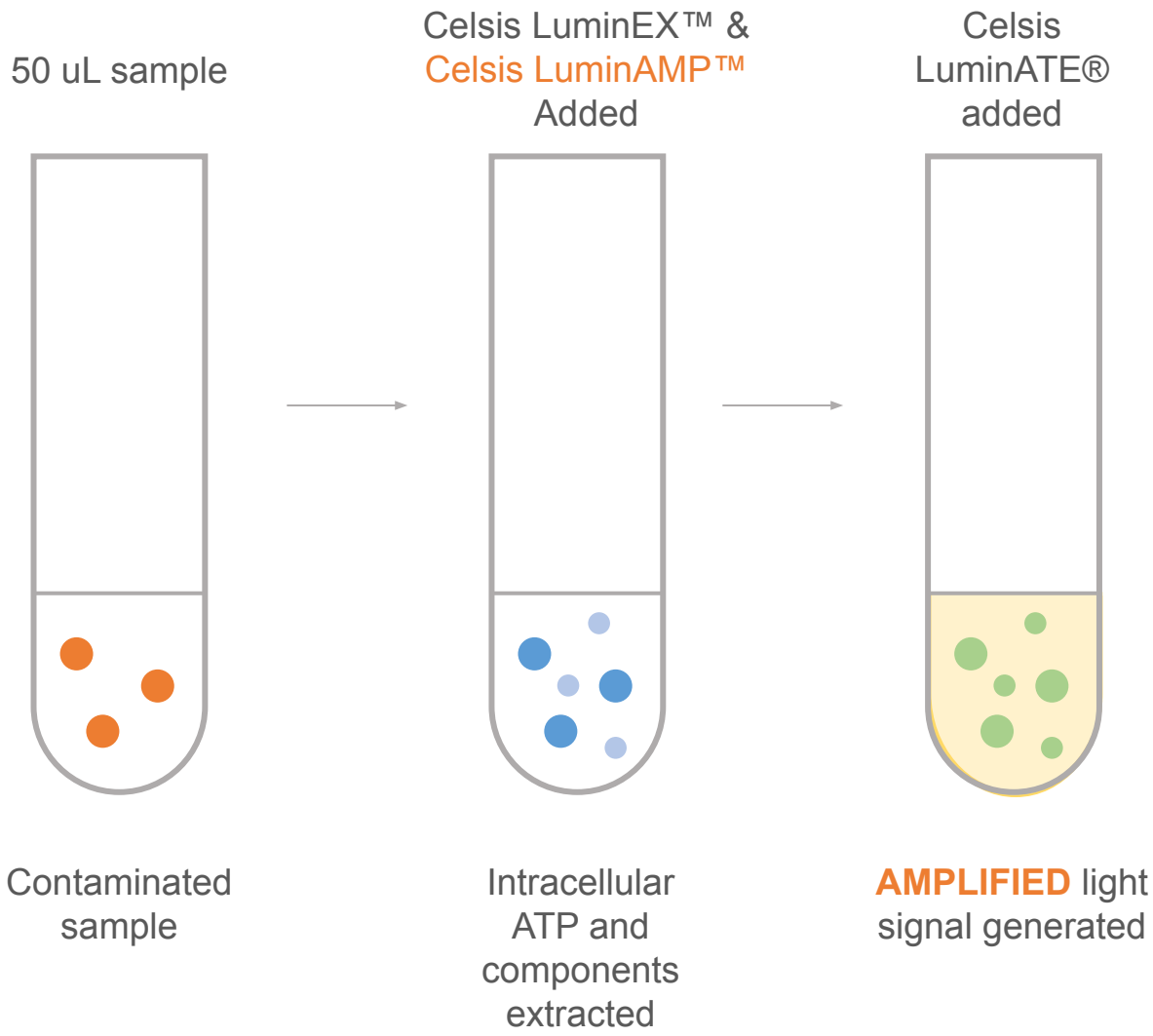


$$ATP + O_2 + Luciferin \xrightarrow{Luciferase, Mg^{2+}} AMP + CO_2 + Oxyluciferin + Pyrophosphate + Light$$

CELSIS AMPISCREEN®
AMPLIFIED ATP BIOLUMINESCENCE

Celsis® ATP-Bioluminescence Reagents

- Two-phase, proprietary enzyme reaction
- All living organisms also contain the enzyme adenylate kinase (AK) as part of their biochemical processes
- Microbial enzymes convert ADP into ATP
- Amplification of ATP levels beyond naturally occurring level.
- Enzymes are not depleted by reaction
- Ability to generate almost unlimited amounts of ATP



ROBUST REAGENTS. RAPID RESULTS.

Celsis® ATP-Bioluminescence Reagents

A rapid microbial detection instrument is only as good as the reagents that power it.

Celsis® utilizes the most advanced class of adenosine triphosphate (ATP) bioluminescence reagents, unlocking new efficiencies for your QC workflow and a new level of confidence in the safety of your product.

Don’t settle for less. Charles River manufactures Celsis AMPiScreen® Pharma reagents to the same high-level quality you build into your own products.

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Method Overview & Applications

CELSIS APPLICATIONS

Celsis® Method Overview

microbial limits

STERILITY

contamination response

USP <61>, <62>; EP 2.6.12

- Products testing negative: pass
- Products testing positive: SOP for enumeration/identification

USP <71>, EP 2.6.1

- Trusted for final product sterility in Pharma market

Non-destructive Test

- Celsis® Enrichment reserved for rapid retest or investigation

PRIMARY CONSIDERATIONS

When Choosing an RMM

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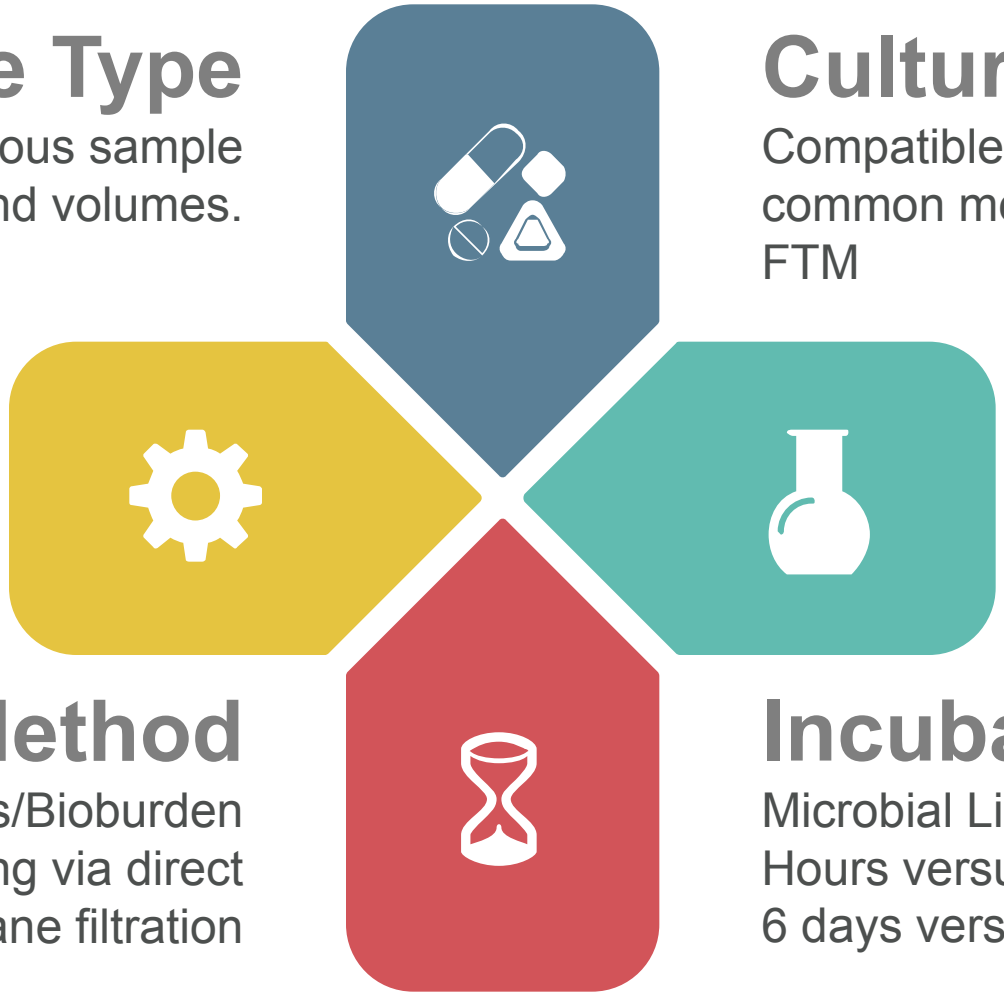
ADAPTS TO CURRENT TEST PROTCOLS

Minimizes Changes to Current Preparation Method

Sample Type

Capable of testing various sample matrices, sizes, and volumes.



Culture Media

Compatible with a wide variety of common media: such as TSB, TAT, and FTM

Test Method

Compatible with Microbial Limits/Bioburden testing and sterility testing via direct inoculation or membrane filtration

Incubation Time

Microbial Limits and Bioburden in 24 Hours versus 5-7 days. Sterility results in 6 days versus 14 days

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FLEXIBLE PROTOCOL FOR BROAD PRODUCT SUITABILITY

Celsis AMPiScreen® Method Overview

Flexible Protocol

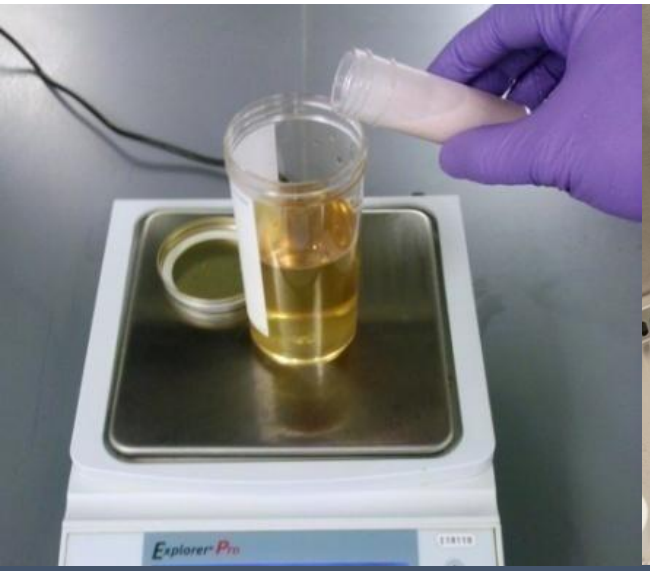
- W/ or w/o filtration
- Varying broth volumes/types
- Soluble / Non-soluble products
- High pH / Low pH products
- Oil / Water based products
- Pigmented products
- Preserved products

Product Matrix Examples

- IV Solutions, Antibiotics, Vaccines
- Tablets, Syrups, Suspensions
- Lotions, Creams, Ointments, Gels
- Medical Devices, Packaging
- Soaps, Detergents, Fabric Softeners
- Toothpaste, Deodorant, Cosmetics
- Ink, Pudding, Juices, Nutritionals

EXAMPLE PROTOCOL – MICRO LIMITS TESTING

Celsis AMPiScreen® Method Overview



Direct Inoculation

- Measure and prepare sample in broth media (typically TAT, TSB, or Letheen).

Membrane Filtration

- Filter sample according to preparation method and transfer membrane to broth media for incubation.

Incubate

- Incubate samples for 24 hours
- For mold detection, add beads and place on linear shaker for 30 minutes after incubation.

Analyze

- Pipette 50µL of incubated sample into cuvettes and load into instrument.
- After ~1 hr automated analysis, collect results.

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celsis®
For Rapid Sterility Testing

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Key Advantages of a Rapid Test Method

TRADITIONAL METHOD VS CELSIS RMM

Key Advantages of a Rapid Test Method

Traditional		Celsis®
Antiquated, Subjective, Visual readout	DETECTION PRINCIPLE	Instrument-based, Enzyme-catalyzed assay
5–7 Days Microbial Limits	TIME (DAYS)	24 Hours Microbial Limits,
Labor Intensive	EASE OF USE	Automated Analysis
CFU or Presence/Absence	METHOD	RLU or Presence/Absence
High Impact, High Cost	RELATIVE TOTAL COST	Less Than Traditional

Traditional
Incubation Method

Celsis®
Rapid Method

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DATA INTEGRITY

A Key Advantage to Rapid Sterility Testing Resulting in Improved Data Integrity position

Subjective evaluation in Tradtional Method

- Based on visual, human analysis
- Four-eyes principle requires additional personnel
- Prone to interpretation and transcription error.
- Single canisters compared against control canister for each media type.

IMPROVED TEST PERFORMANCE

A Key Advantage to Rapid Testing Resulting in Improved Data Integrity position

An example where turbidity is a poor indicator of microbial contamination.

Which are sterile and which are contaminated?

Samples 1 and 2 are **sterile.**

Samples 3 and 4 are **contaminated.**

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DATA INTEGRITY

Objective Evaluation in Celsis Rapid Detection

- Based on instrument analysis.
- Automation allows walk-away results.
- Automatic results reporting and export removes possibility of interpretation or transcription errors.
- Duplicate cuvettes prepared for each sample compared against duplicate control cuvettes.

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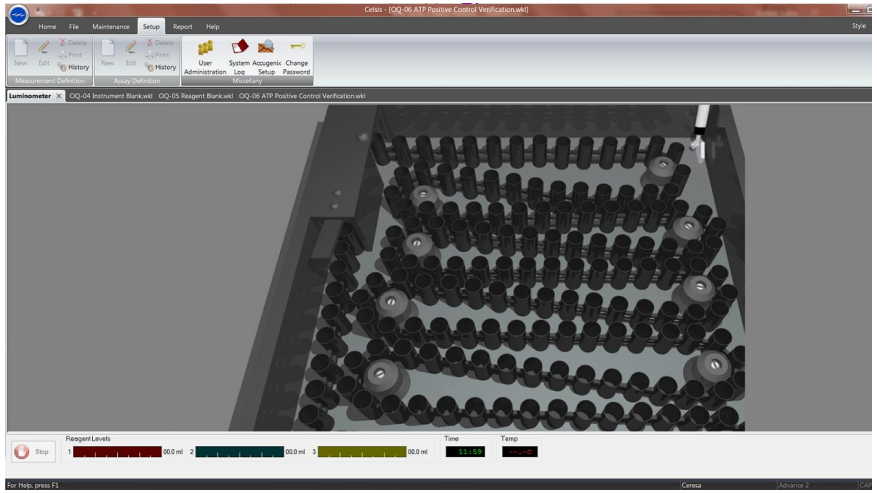
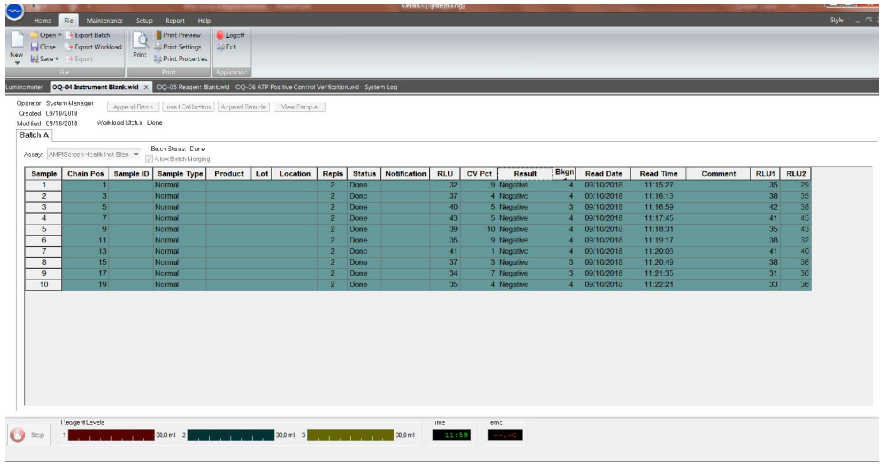
RESULTS INTEGRITY

Subjectivity vs Objectivity: Celsis.im software





✔ **ASSAY AUTOMATION**

- Precisely controls reagent volumes and reaction timing

✔ **OBJECTIVE RESULTS:**

- Interprets results against validated parameters
- Provides multiple reporting options

✔ **21 CFR Part 11 compatibility**

✔ **Compatibility up to Windows 10 Pro**

✔ **Archived data protects data integrity**

✔ **Administrator right and users roles/permission structure**

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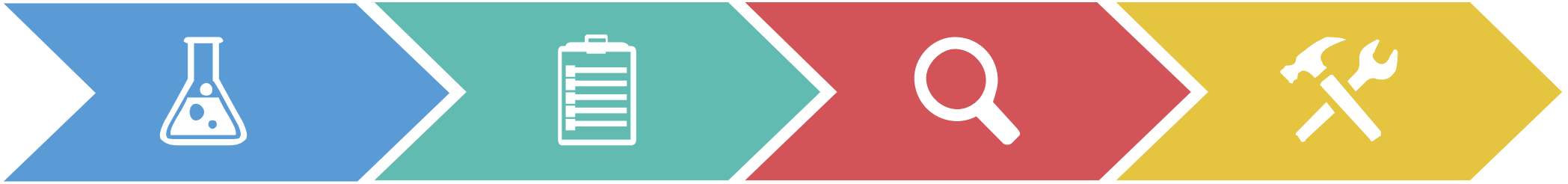
celsis®
The support you need from start to finish, and beyond.

YOUR SUCCESS IS OUR SUCCESS

Industry Leading Expertise And Support



APPLICATION DEVELOPMENT

- Charles River Application & Development Labs
- Feasibility and Sample Evaluation Testing

VALIDATION

- IQ / OQ completed with installation
- PQ documentation and validation guides
- Equivalency Report Available
- Coming soon: Method Suitability Services and Protocols

REGULATORY

- Drug Master Files and Technical Reports
- Strong track record of regulatory acceptance and compliance experience

TECHNICAL SUPPORT

- Three days of on-site training
- Experienced Technical Account team
- Global network

OPERATIONAL IMPACT OF CELSIS®

Reduced cost of manufacturing

Reduced inventories

Financial Savings

Earlier response to contamination events

Experienced global support through Charles River

LEADING COMPANIES TRUSTING CELSIS® DETECTION

Proven and In Use by Pharma and Personal Care Product Manufacturers

NOVARTIS

gsk

Roche

janssen

AVON

Unilever

ESTĒE LAUDER

P&G

STERIS®

COLGATE-PALMOLIVE

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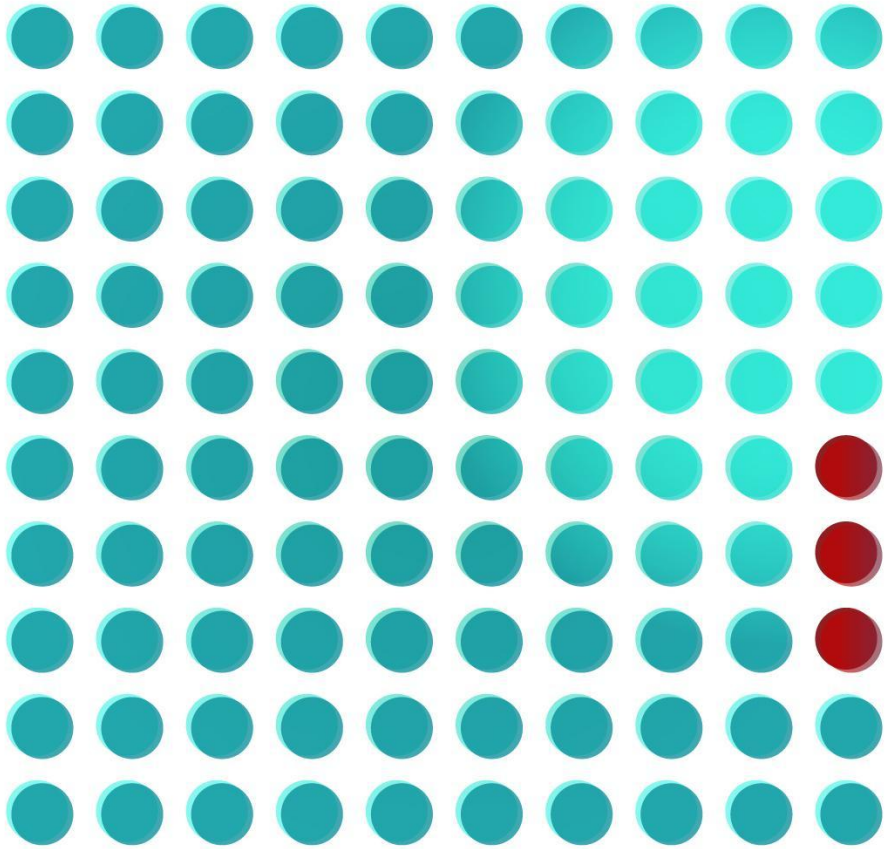
CRITICAL INFORMATION TO RELEASE PRODUCT FASTER

Increased Efficiencies of a Qualitative Screening Assay



Products test negative: rapid release

REDUCED INVENTORY AND COST TO MANUFACTURE

Products test positive: rapid response

REDUCED CONTAMINATION COSTS

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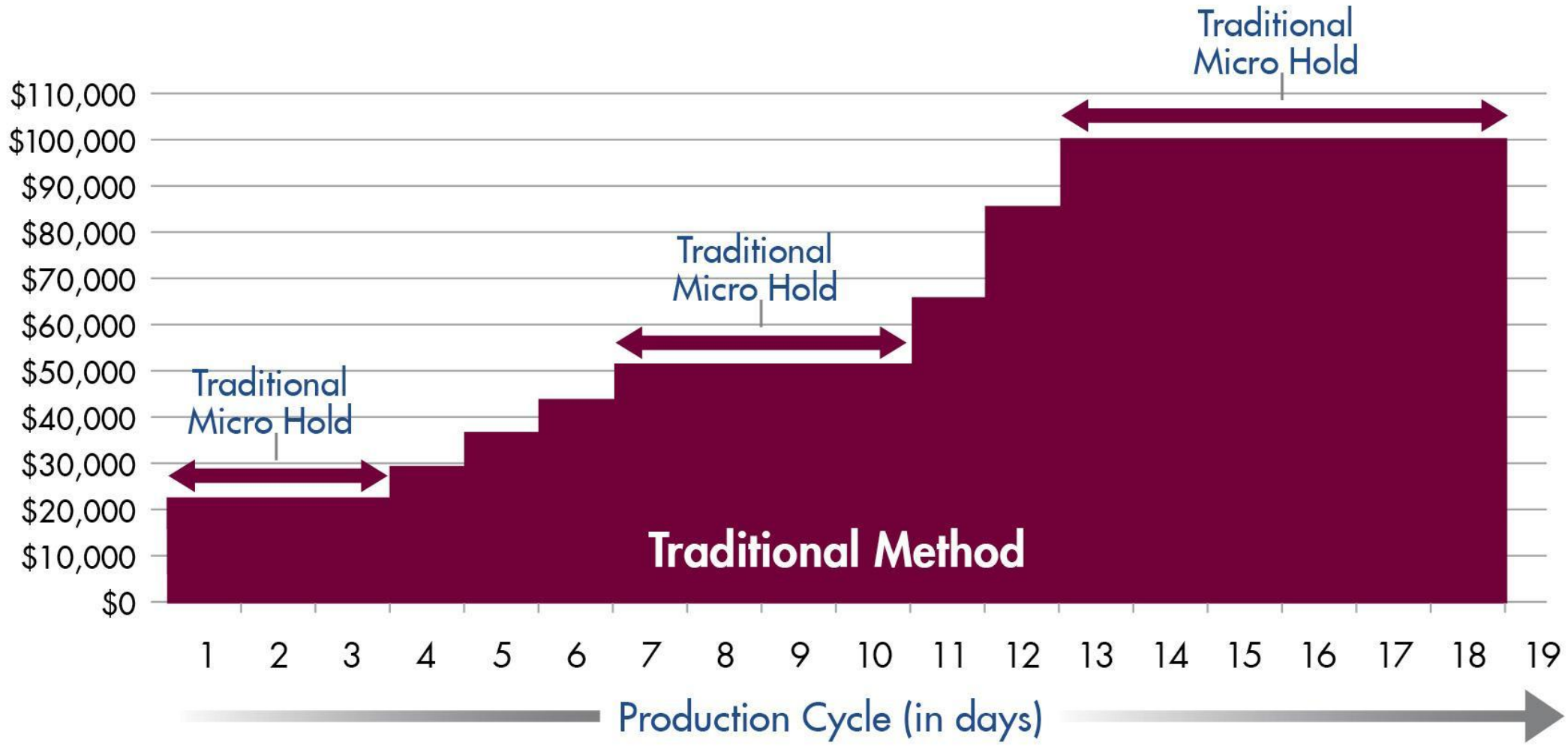
REDUCING INVENTORY AND LEAD TIMES

The Cost Savings from Charles River RMMs



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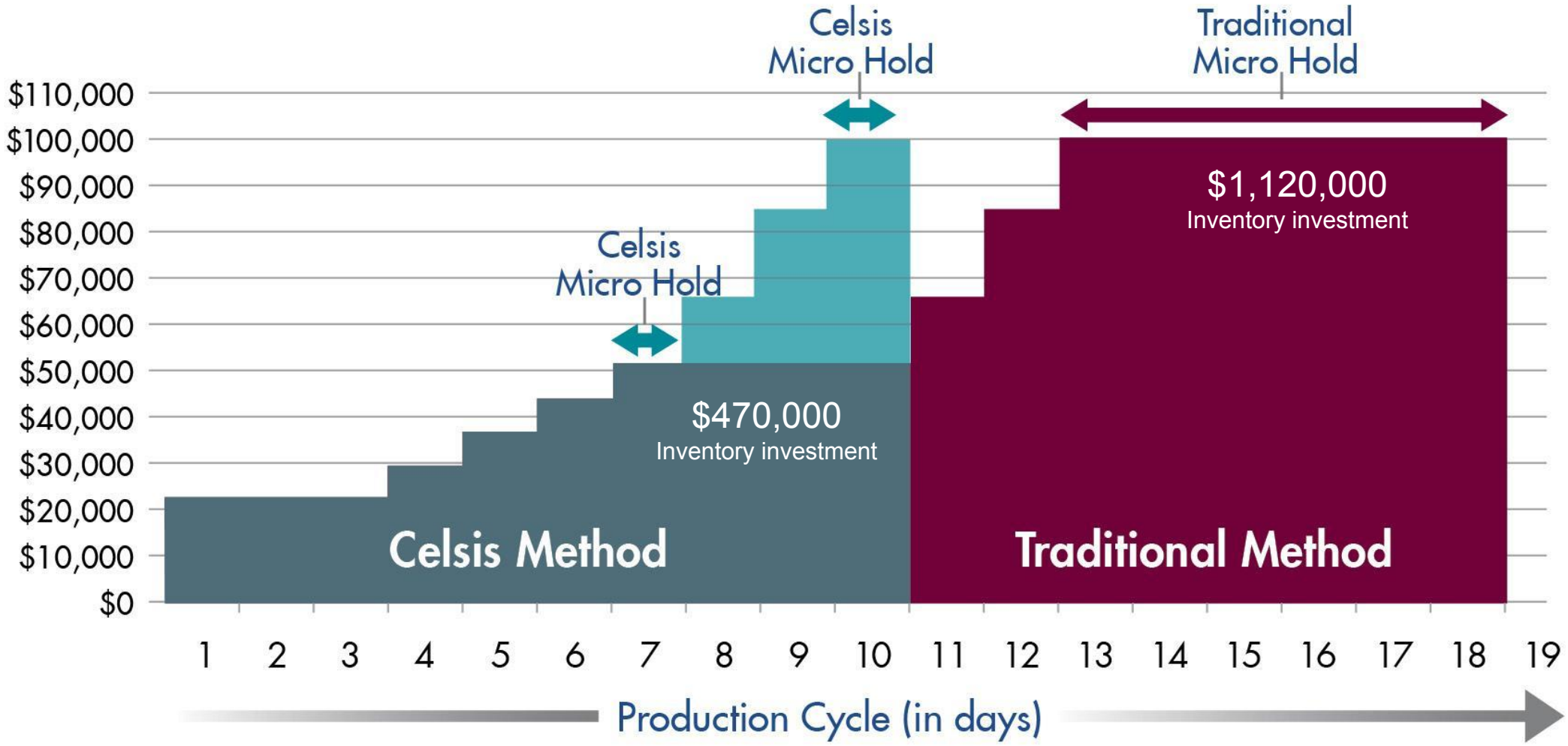
REDUCING INVENTORY AND LEAD TIMES

The Cost Savings from Charles River RMMs



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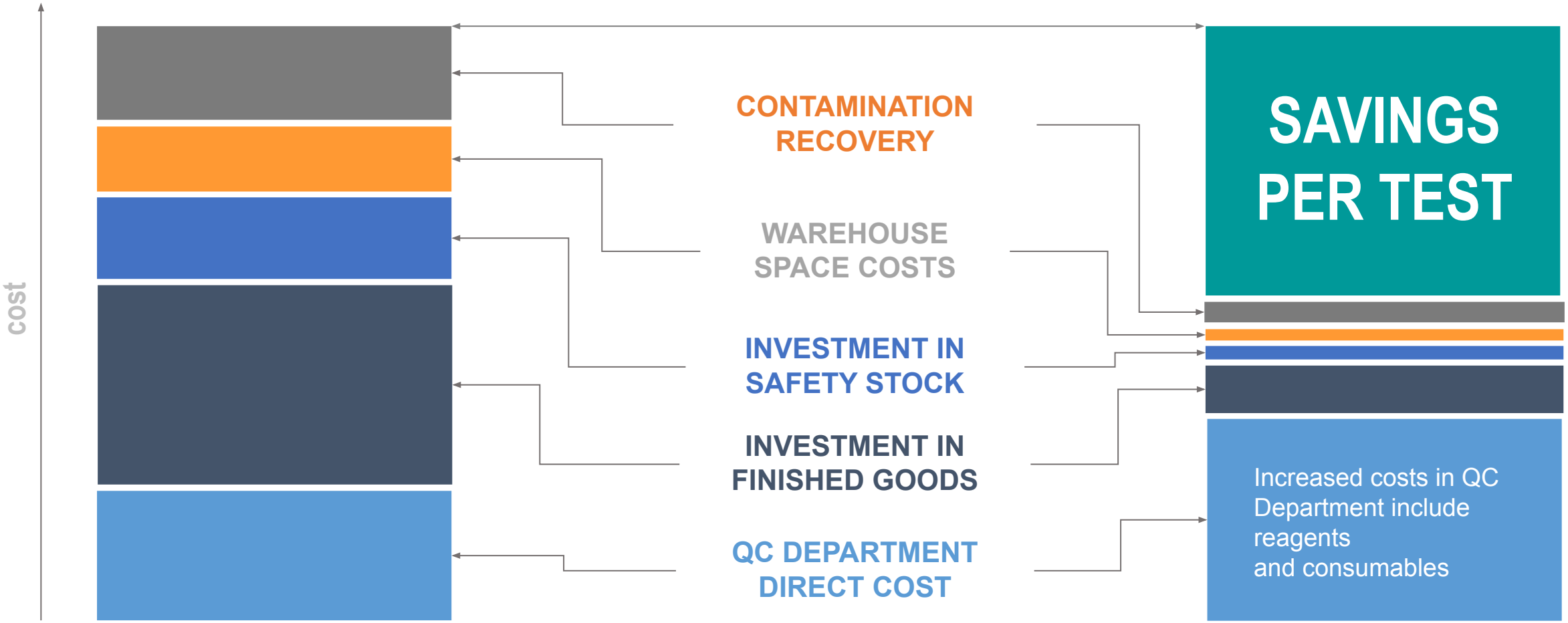
HIDDEN COSTS ADD TO TRUE COST PER TEST

The Cost Savings from Charles River RMMs



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FINANCIAL IMPACT ASSESSMENT

The Cost Savings from Charles River RMMs

Using **readily available** financial and QC data, the following can be determined:

- Net Present Value over 5 years
- Payback Period Calculation
- Annual Containment Savings
- Calculates single and multi-site implementations

Business Specific Input	
Begin first period	Jun-15
Cost of Capital	10.0%
Stock carrying cost	20.0%
Value of Daily Finished Goods Output ($,£,€)	100,000
Space needed for daily output (Sq.Unit.)	1,500
Warehouse space cost ($,£,€)/Sq Unit/Annum)	10.00
Lab technician salary & benefits ($,£,€)	60,000

Testing	
Validation tests per product	25
Number of products for validation	20
Number of tests per year	5,000
Quarantine days -Current	5
Quarantine days -Celsis	1
Current test cost	4.00
Celsis test cost	7.75

Fixed Transfer Costs	
Equipment purchase	97,657
Validation Support	

Calculated Results	
Five-year Net Present Value ($,£,€)	**1,215,591**
Payback Period (Months)	**7.88**
Annualized Containment Savings ($,£,€)	**100,000**

Risk Management of Contamination Events	
Frequency (Occur./Yr)	0.50
Loss Factor	50%
Current days to detection	5
Proposed days to detection	1

Include Safety Stock Savings?	
Enter Yes or No	yes

Implementation by Period	
Period 1	50.0%
Period 2	100.0%
Period 3	100.0%
Period 4+	100.0%

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SUMMARY AND NEXT STEPS

01

Celsis Rapid Microbial Detection…

builds on experience of traditional methods, but offsets the limitations.

02

Celsis AMPiScreen Method…

offers simplicity, flexibility, and rapid results.

03

Charles River Microbial Solutions Support…

provides a global partner to achieve successful implementation.

NEXT STEPS

- Establish multi-function team and project timeline
- Complete and review Financial Impact Assessment
- Review products for validation and implementation

CONTACT US

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APPENDIX

Additional Information

RMM TECHNOLOGY SELECTION

Growth Based Methods Detectable signal is achieved after a period of growth

- Amplified ATP Bioluminescence
- CO2 Production
- Flow Cytometry
- Fluorescence-Assisted Colony Counter
- Standard ATP Bioluminescence
- Digital Imaging Technology

Direct Measurement: Individual cells are differentiated and visualized

- Flow Cytometry
- Solid Phase cytometry

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REGULATORY OVERVIEW

Industry Leading Expertise And Support

Regulators do not pre-approve RMM technologies; the user is responsible for seeking approval of use with their products, process, and method.

Already in Use

- A growing number of companies have received approval for the use of Celsis for finished product testing using various submission strategies

Guidance for the Validation of Rapid Microbial Methods

- PDA TR33
- USP<1223>
- Ph. Eur. 5.1.6

PRIMARY CONSIDERATIONS IN SELECTING AN RMM TECHNOLOGY

TECHNOLOGY	PRODUCT APPLICATION	TIME TO RESULT	THROUGHPUT	VIABILITY	ADOPTION
Amplified ATP Bioluminescence	Broad (Celsis)	18-24 h	High	Non-destructive	800 Global Instruments
CO_2 Production	Broad	48-72 h	Low	Non-destructive	Limited Clinical
Solid & Flow Cytometry	Limited	9-50 h	Low	Destructive	Limited
Fluorescence	Limited	24-48+ h	Low	Non-destructive	Limited
ATP Bioluminescence	Limited (filter)	24-48+ h	Low	Non-destructive	Limited

TIERS OF REGULATORY REQUIREMENTS

Appendix A

	US / FDA / USP		EU / EMA / EP	
	Validation Required	Submission required	Validation Required	Submission required
OTC Over the Counter	✓	No	✓	No
In-process Testing	✓	Not typically unless micro commitments made in filing	✓	Typically ✓
Non-sterile Regulated	✓	✓	✓	✓
Sterile Regulated	✓	✓	✓	✓

PDA TR33 GUIDANCE

Appendix B

PDA TR33 Validation Criteria	Qualitative Method	User or Supplier Demonstrated	Celsis Approach	
Equivalence / Comparative Testing	Yes	User	Equivalency Protocol	✓
Limit of Detection	Yes	User	Generated from Equivalency Protocol	✓
Method Suitability	Yes	User	Typical Celsis Sample Effects	✓
Specificity	Yes	User	Typical Celsis Spiking studies	✓
Ruggedness	Yes	Supplier	Technical Report TR120407-04	✓
Robustness	Yes	Supplier	Technical Report TR120408-02	✓
			Drug Master File	✓

PROACTIVE QUALITY SYSTEMS REDUCE RISK

What if you do find a positive result?

The cosmetic products industry has a known history of recall notices that name the following organisms as microbial contaminants*: B. cepacia, P. aeruginosa, S. aureus, E. coli., K. pneumoniae,* and *S. marcescens*.

Aside from the obvious concern for consumer safety, a microbial contamination is also costly in terms of immediate financial impact and longer-term damage to the brand's reputation.

So how can you reduce the risk of a product recall associated with these and other known harmful organisms?

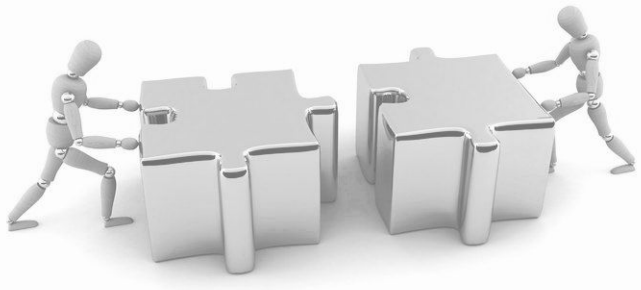
- Environmental monitoring
- Accurate and reliable microbial identification
- Tracking and trending EM data

THE IMPORTANCE OF ACCURATE IDENTIFICATIONS & EM

- The first step in most risk-reduction approaches is identification and characterization of the objectionable organism.
- The next step is accurate identification, which can only occur if the organism is present in the microbial library that is referenced.
- Environmental monitoring (EM) is a fundamental aspect of cGMP compliance and is a proven strategy for contamination risk mitigation for cosmetic manufacturers.
- Accurate identification of environmental isolates plays an important role in this strategy because it helps record the routine flora of the facility and allows the quality system managers to detect and analyze any deviations from the norm.

The Environmental Monitoring Program

- Measures and documents the **State of Control** of the facility
- Quality of the environment
- Acts as early warning surveillance system



The Isolate of Concern

- **Risk management -** Evaluate level of risk
- Origin of contamination
- Is the isolate objectionable?
- CAPA planning to mitigate risk

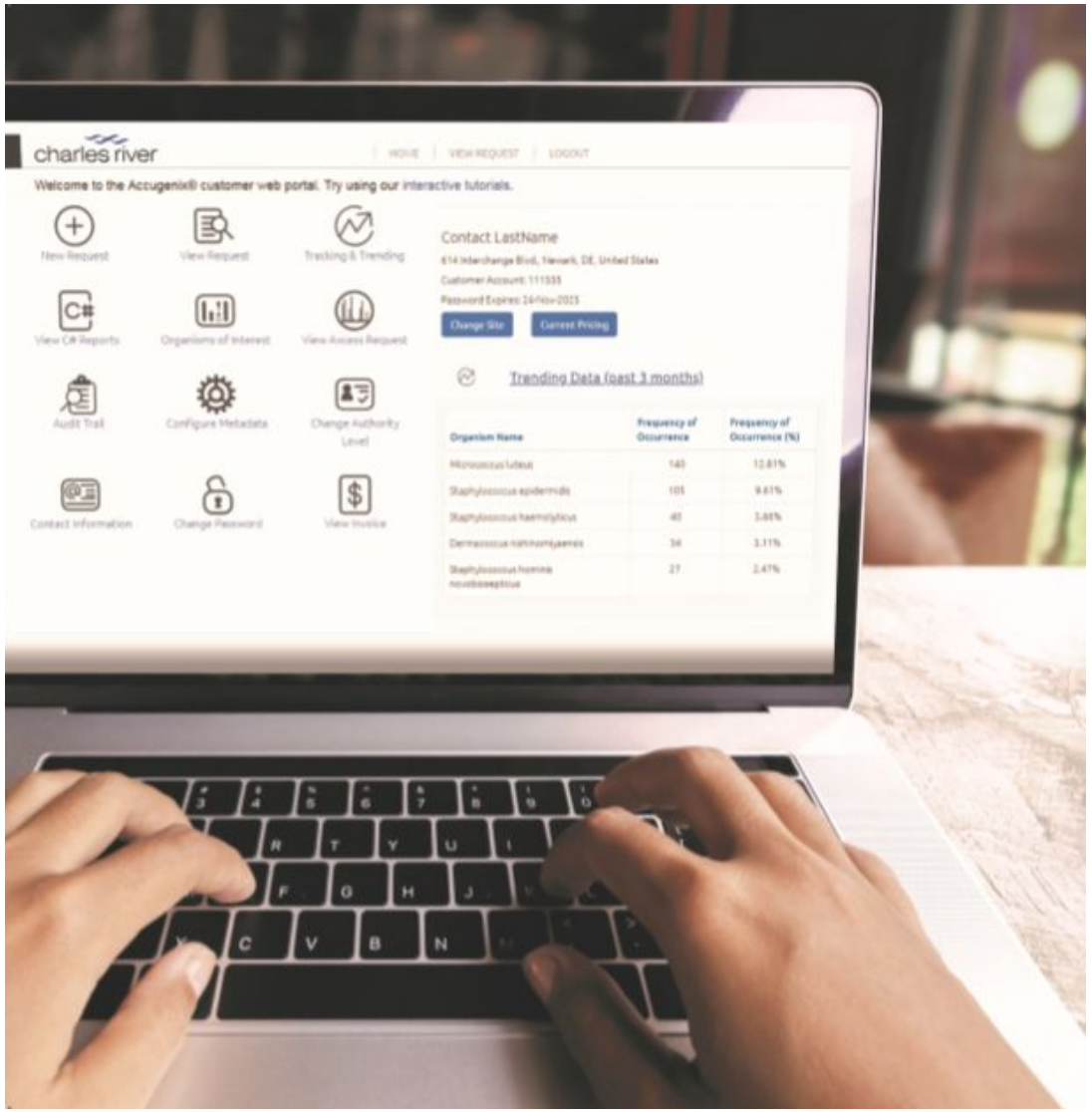
WHY TREND ORGANISMS?

Turning Raw Data into Actionable Information

When you have confidence in your ID results, you can gain a better understanding of your manufacturing environment and the ability to aggregate and trend EM data.

But collecting and managing this data can be difficult and time-consuming, which is why having the right tool to automate these processes can lead to significant time (and cost) savings.

SUPERIOR DATA LEADS TO SUPERIOR CONTROL



IMPROVED TEST METHODS

RECORDS MANAGEMENT

DATA INTEGRITY