Accelerating Sterility Testing: A Case Study on Implementing the 7-day Celsis Method

Method Implementation and Lessons Learned

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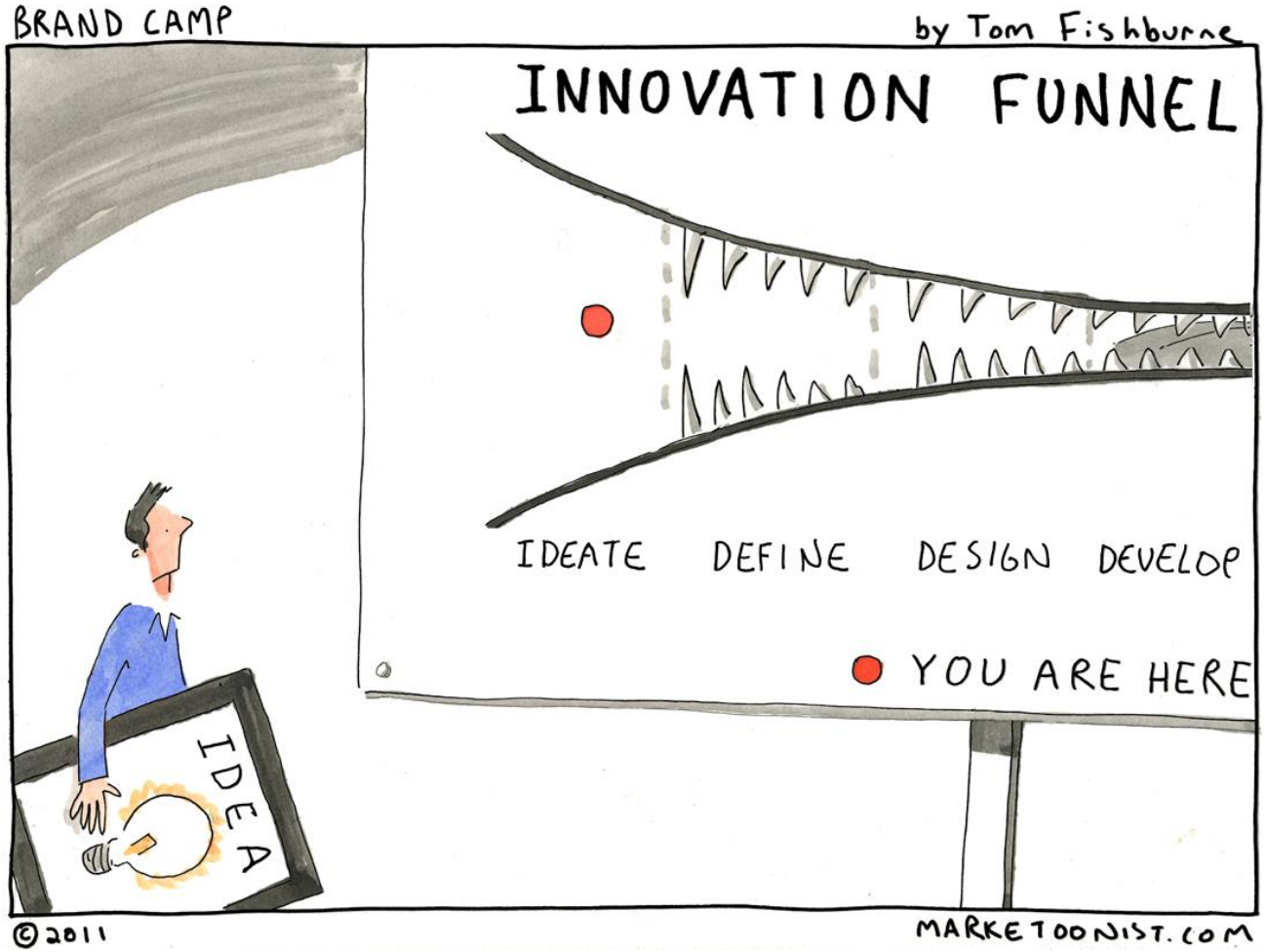
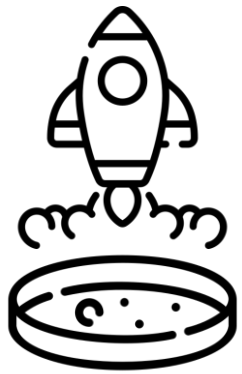
Introduction

Implementing new technologies is challenging



General Approach to adopt an Alternative Microbiological Method

The 9-step approach

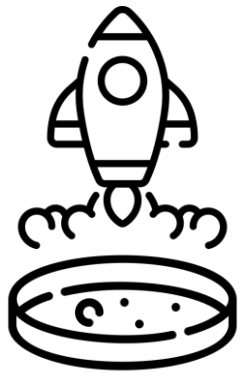


1. Identify business need
2. Define application
3. Identify requirements
4. Compare technologies
5. Business case
6. Proof of concept
7. Validation at pilot site
8. Global deployment
9. Considerations for regulatory strategy

For more details see the 2020 BioPhorum publication *A framework for the evaluation, validation and implementation of alternative and rapid microbiological testing methods*

General Approach to adopt an Alternative Microbiological Method

The 9-step approach



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The following slides demonstrate the 9-step approach to implement the Celsis method at Roche

For more details see the 2020 BioPhorum publication *A framework for the evaluation, validation and implementation of alternative and rapid microbiological testing methods*

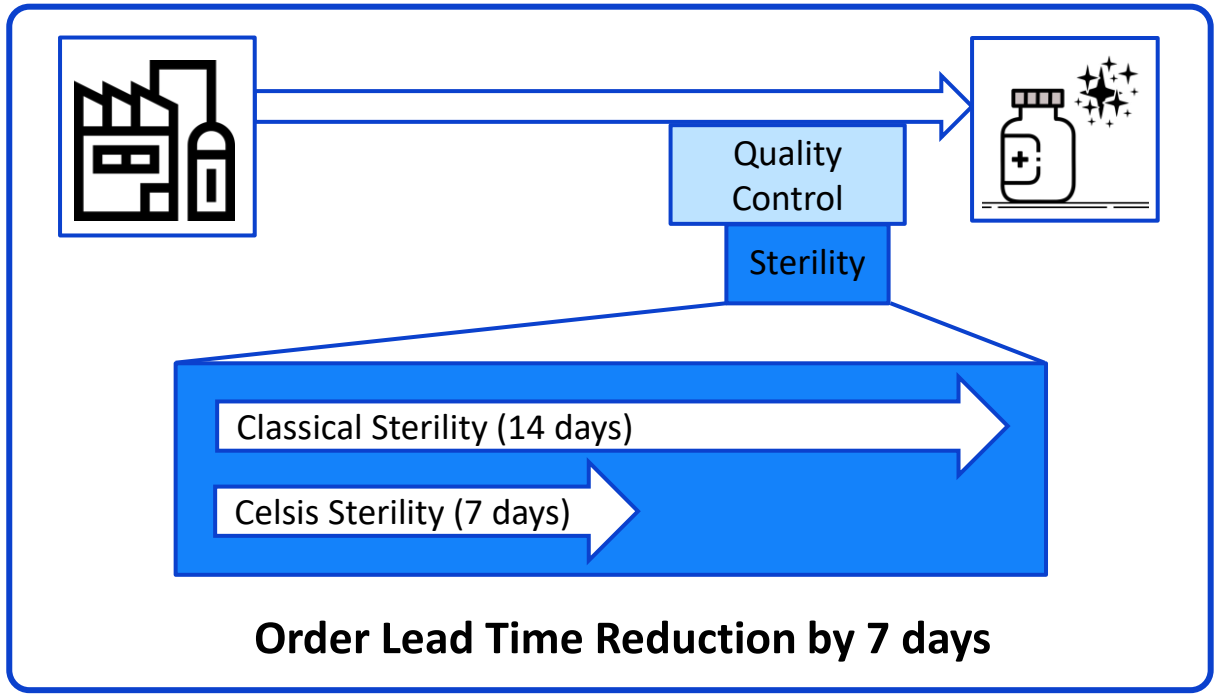
9-Step Approach

Step 1 - Identify business need

1 2 3 4 5 6 7 8 9

Identify business need

- Faster time to result
- Improvements in data integrity
- No second verified needed
- Earlier intervention in case of an OOS
- State-of-the-art QC operations



9-Step Approach

Step 2 - Define application

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Define application

- Replacement of compendial sterility test
- Qualitative method
- Release testing of drug product

9-Step Approach

Step 3 - Identify requirements

1 2 3 4 5 6 7 8 9

Identify requirements

Critical requirements:

- At least 50% reduction in time to result
- Membrane filtration technique
- Suitable for large & small molecules
- Software must be 21 CFR 11 compliant
- Mature technology
- Possibility to determine ID in case of contamination
- Good vendor support

Nice to have requirements:

- Equipment easy to use
- Increased sensitivity
- Increased automation
- Connection to LIMS

9-Step Approach

Step 4 - Compare technologies

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Compare technologies – landscaping and candidate selection

Growth-based, *e.g.*

- Detection of CO_2
- Digital imaging of microcolonies
- Microcalorimetry

Viability-based, *e.g.*

- Flow Cytometry

Cellular component-based, *e.g.*

- ATP biofluorescence

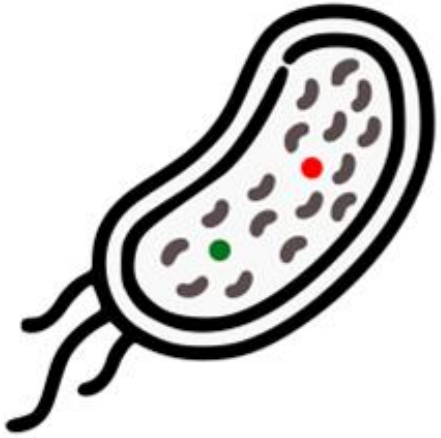
9-Step Approach

Step 4 - Compare technologies

1 2 3 4 5 6 7 8 9

Celsis technology background

Step	Compendial method	Celsis method
Filtration	Membrane filtration. Rinse and addition of growth media (TSB and FTM)	
Incubation	Incubation for **14 days**	Incubation for **7 days**
Analysis	Detection by **visual inspection** of macroscopic growth	**Additional sample preparation step**. Detection by **bio-luminescence readout**



- AK (Adenylate kinase)
- ATP (Adenosine triphosphate)

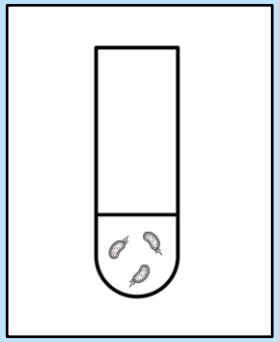
9-Step Approach

Step 4 - Compare technologies

1 2 3 4 5 6 7 8 9

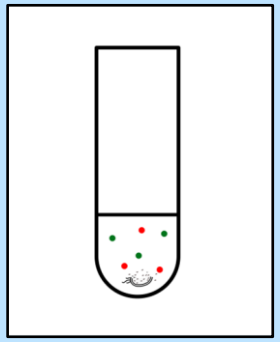
Celsis technology background

50 µL sample



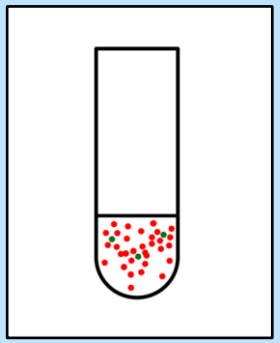
Contaminated sample

Cell lysis: Extraction reagent is added



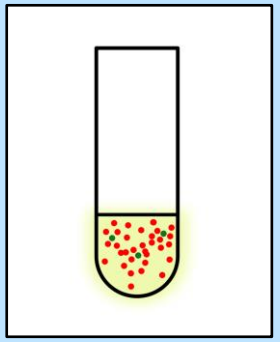
Intracellular components like ATP and AK are released

Amplification reaction: Reagent containing ADP is added



Cellular enzyme AK converts ADP to ATP

Bioluminescence reaction: Reagent containing luciferase is added



Light generated is measured using the Celsis luminometer

Increased sensitivity:

If ADP is added in large access, adenylate kinase (AK) generates significantly higher levels of ATP.

Amplification reaction:

2 ADP $\xrightarrow{\text{AK}}$ AMP + **ATP**

9-Step Approach

Step 5 – Business case development

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Business case

Next to the financial aspects (ROI) the following aspects must be considered as well:

- Efficiency gains
- HA expectations
- User/industry feedback

9-Step Approach

Step 6 – Proof of concept

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Proof of concept / feasibility studies / pre-validation

Customize the method (pre-validation)

- Shaking of sterility containers
  - Ensure detection of aggregate forming microorganisms
- Sample preparation
  - Removal of the aliquot from the sterility containers

Feasibility study (proof of concept)

- Time to result for worst case microorganisms
  - Include *C. acnes* and stressed microorganisms
- Product interference
  - Evaluate false positive or false negative results

9-Step Approach

Step 7 – Validation at pilot site

1 2 3 4 5 6 7 8 9

Validation at pilot site

Primary validation

- Without product, performed at pilot site (in cooperation with vendor)
- 12 organisms; spike levels of 0.1 / 1 / 10 CFU
- Demonstrates that Celsis is non-inferior

Method suitability test

- Evaluation of growth-inhibiting properties
- Celsis-specific product-interference testing

9-Step Approach

Step 8 – Global deployment

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Global deployment / qualification of additional laboratories

Method transfer

- Performed for each DP release testing site
- Verification of primary method
- Demonstrates the receiving site is able to run the Celsis analysis

9-Step Approach

Step 9 – Considerations for regulatory strategy

1 2 3 4 5 6 7 8 9

Consideration for regulatory filings and implementation strategy

Various filing strategies are valid

1. Post-approval-change of already commercially marketed products
2. Filing as part of the launch of a new product
3. Filing in development phase of a new product (CTA)

Specific country requirements, *e.g.*

- In-country testing

9-Step Approach

Step 9 – Considerations for regulatory strategy

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Post approval Change - pilot product

- Pilot product only manufactured at one site with moderate production
- Regulatory Strategy
  - Post approval submission without prior HA interaction
  - Wave 1: US, EU, and CH to receive feedback from ‚major' HAs (Oct 2019)
  - Wave 2: Rest of world (Apr 2020)
  - File Celsis as primary method, compendial remains as a back-up

9-Step Approach

Step 9 – Considerations for regulatory strategy

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Post approval change of commercially marketed products

- Bundled with other QC technologies
- Combined with filing opportunities, *e.g.* Life cycle control update
- Out of scope: products at the end of the life cycle and products manufactured at CMOs
- Implementation after final green light, no dual testing
- Switch from compendial to Celsis usually 2-4 years after first submission

9-Step Approach

Step 9 – Considerations for regulatory strategy

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Filing as part of the launch of a new product

- Switch to Celsis together with market implementation
- Easier compared to PAS

9-Step Approach

Step 9 – Considerations for regulatory strategy

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Filing in development phase of a new product (CTA)

- Currently not planned
- No business case for Celsis during clinical phase

Project Milestones

Timeline

- Technology evaluation
- Business Case
- Pre-validation
- Feasibility study
- Method validation
- Submission of pilot
- Method transfer
- Post approval changes of marketed products
- Filing as part of new launches

Project Milestones
Where are we today

Where are we today

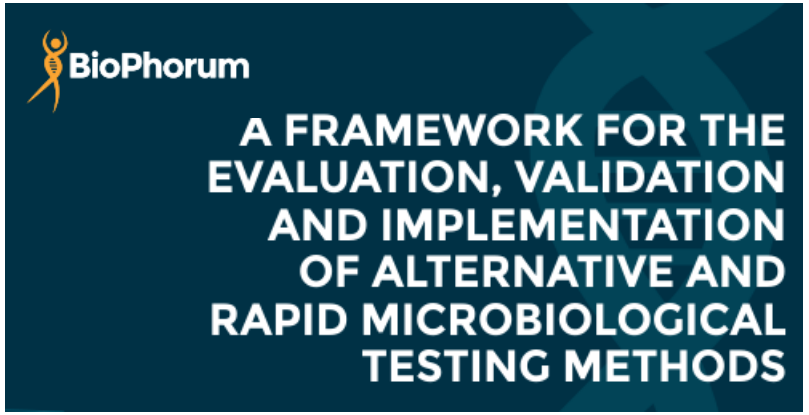
- Celsis implemented for 5-10 launch products
- Celsis submitted for more than 10 commercial products

Lessons Learned

Summary

- All health authorities accepted Celsis
- Resource planning
  - Dedicated team and sufficient budget needed to implement a new microbio technology
- Membrane filtration
  - Product interference detected for some products → increased background signals
  - Optimize rinsing procedure might be required
- Very long approval times (worldwide)
  - Post approval changes can take 2-4 years until final green light
  - Implementation at launch (BLA/NDA) is much easier and faster

Thank you
for your attention



Link to BioPhorum

PDA JPST PDA Journal of Pharmaceutical Science and Technology

Other | Technology/Application

Rapid Sterility Test Systems in the Pharmaceutical Industry: Applying a Structured Approach to their Evaluation, Validation and Global Implementation

PDA Journal to BioPhorum

Doing now what patients need next