Creating GMP in an Academic Research Setting and Clinical Hospital Environment – Challenges and Lessons Learned at the NIH

Anna F. Lau, Ph.D., D(ABMM)
Chief, Sterility Testing Service
Department of Laboratory Medicine
Clinical Center
National Institutes of Health

Disclosures

- None

- This work was supported by the Intramural Research Program of the National Institutes of Health. The content is solely my responsibility and does not represent the official views of the National Institutes of Health.

National Institutes of Health

Turning Discovery Into Health

- World's largest biomedical research institute
- 27 institutes/centers (ICs)

NIH Clinical Center (CC)

NIH Clinical Center

- **Research hospital** dedicated solely to bench to bedside clinical research. First in human trials.
- Every patient is enrolled in a clinical trial
- Novel therapeutics developed since 1980s
  - Investigational New Drugs (INDs)

Variety of Products Manufactured at the NIH

Cell & Gene Therapy Products (n=24)		
Anti-BCMA HC CAR-Transduced Autologous T Cells	BSS® Plus (BSS+) Media	Monocytes/Granulocytes
Genetically Modified PBL Cell Therapies	CD33 CART Drug Product	CD34 XSCID
Cryopreserved Cellular Products with and without Cryostor Rinse Off	Cryopreserved CD34, final product, post thaw bag, and post thaw vial	Red Blood Cells Cryopreservation (Malaria vaccine)
FGFR4 CAR-T Cells	Cell lysate in PBS	Young TIL Cells
Induced pluripotent stem cells	Red Blood Cells (Sickle Cell Vaccine)	Infused FN-RBCs in Saline
Retinal pigment epithelium	Anti-BCMA HC CAR-Transduced Autologous T-Cells	Dendritic Cells RPMI Basal Medium

PET Radiolabeled Drugs (n=5)
C-11 NNC (+24 h and +96 h)
F-18 DOPA (+24 h and +96 h)
Ga-68 DOTATATE (+24 h and +96 h)
O-15 water (+24 h and +96 h)
[11C]MC1 Injection (+24 h and +96 h)

Raw Materials (n=4)
Infusion Bag Media
CryoStor CS10
Cryostar CS5 cryopreservative media containing 5% DMSO
200 Proof Ethyl Alcohol, Absolute (Dehydrated)

Viral Vector (n=5)

Long History of Sterility Testing at the NIH

Clinical microbiology lab in DLM

First in human trials

Expansion of INDs

1980s **1990s** **2000s**

Sterility testing in clinical micro USP<71> Tedious, labor intensive, slow

New clin micro director switches to sterility testing using automated blood culture bottles

2004

Comparative Study > Cytotherapy. 2004;6(3):183-95. doi: 10.1080/14653240410005997.

Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products

H M Khuu [1], F Stock, M McGann, C S Carter, J W Atkins, P R Murray, E J Read

2006

Comparative Study > Transfusion. 2006 Dec;46(12):2071-82. doi: 10.1111/j.1537-2995.2006.01041.x.

Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR-compliant method

Hanh M Khuu [1], Nayana Patel, Charles S Carter, Patrick R Murray, Elizabeth J Read

CO2 Respiration = Blood Culture Systems

- In every clinical microbiology laboratory
- Designed for automated detection of bloodstream infections

BacT/ALERT, BioMerieux

Clinical branch

Industry branch

- Different media bottles marketed
- Dual-T instrument; 30-35°C and 20-25°C

BACTEC, Becton Dickinson

Clinical branch only
35-37°C

VersaTREK, ThermoFisher

Clinical branch only
35-37°C

Comparative Study > Cytotherapy. 2004;6(3):183-95. doi: 10.1080/14653240410005997.

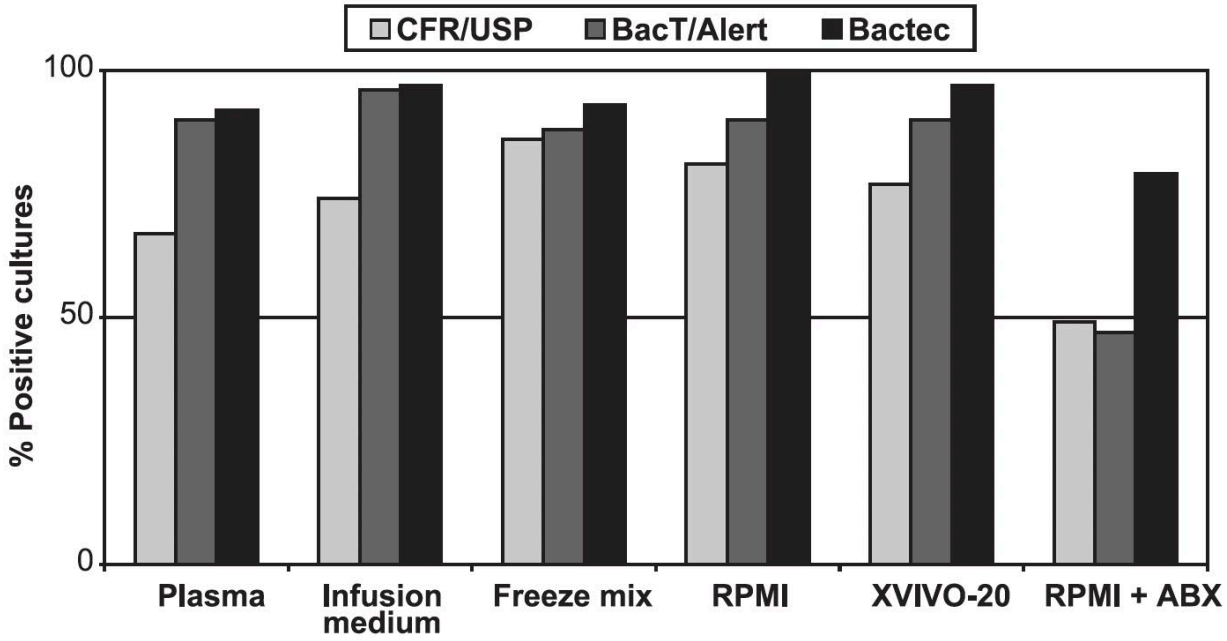
2004

Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products

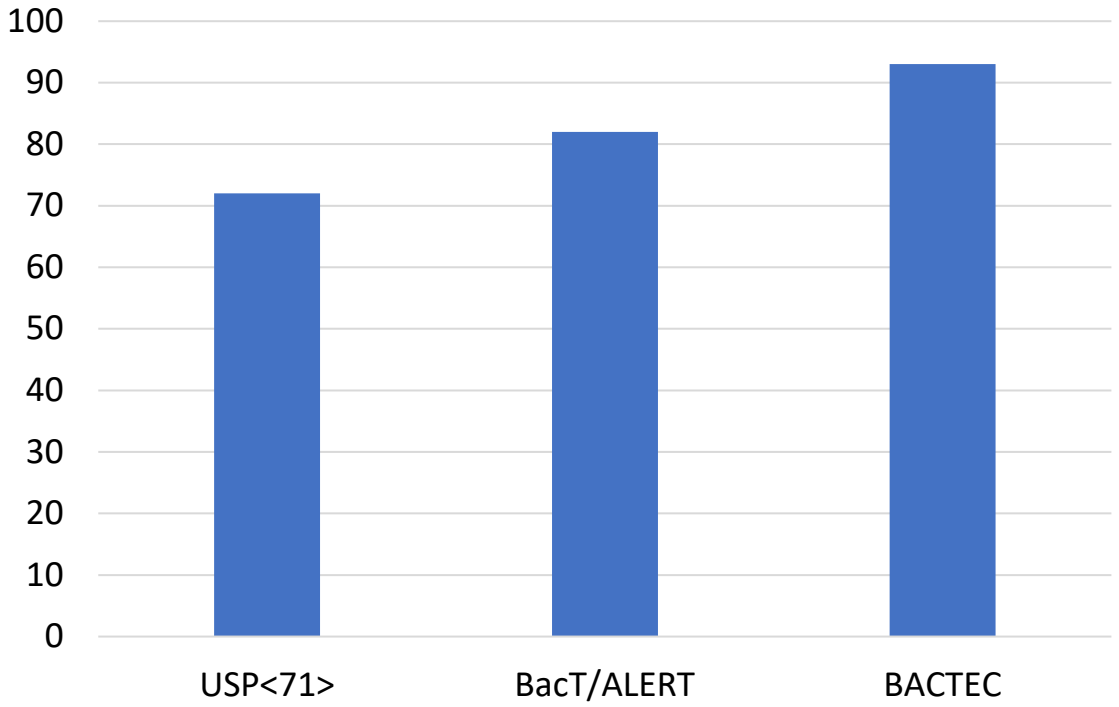
H M Khuu [1], F Stock, M McGann, C S Carter, J W Atkins, P R Murray, E J Read

- Mononuclear cells in 6 different matrices
  - Plasma, infusion medium, freeze mix, RPMI, XVIVO-20, RPMI+ABX
- 10 European Pharmacopeia organisms
  - 10 CFU and 50 CFU
- 3 methods = USP<71>, BacT/ALERT, BACTEC

Sensitivity by matrix



Overall sensitivity



- Overall, significant faster time to positivity of respiration methods compared with USP<71>

Khuu et al (2004), Cytotherapy

Comparative Study > Transfusion. 2006 Dec;46(12):2071-82.
doi: 10.1111/j.1537-2995.2006.01041.x.

2006

Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR-compliant method

Hanh M Khuu [1], Nayana Patel, Charles S Carter, Patrick R Murray, Elizabeth J Read

- 36-month real time parallel evaluation of USP<71> vs automated respiration method (BacT/ALERT or BACTEC)
- 1,617 samples (in-process and final)
- Rate of true positivity equivalent between USP<71> and automated respiration method
- USP<71> high false positive (7.3% vs 0.2%)
- Automated systems faster time to detection

Comparative Study > Cytotherapy. 2004;6(3):183-95. doi: 10.1080/14653240410005997.

2004

Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products

H M Khuu [1], F Stock, M McGann, C S Carter, J W Atkins, P R Murray, E J Read

Comparative Study > Transfusion. 2006 Dec;46(12):2071-82.

doi: 10.1111/j.1537-2995.2006.01041.x.

2006

Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR-compliant method

Hanh M Khuu [1], Nayana Patel, Charles S Carter, Patrick R Murray, Elizabeth J Read

Long accepted by FDA for all NIH INDs (DMF regardless of product type)

Long History of Sterility Testing at the NIH

Clinical microbiology lab in DLM

First in human trials

Expansion of INDs

1980s **1990s** **2000s** **2015**

Sterility testing in clinical micro
Gold standard method
Tedious, labor intensive, slow

New clin micro director switches to sterility testing using automated blood culture bottles

2004

Comparative Study > Cytotherapy. 2004;6(3):183-95. doi: 10.1080/14653240410005997.

Comparison of automated culture systems with a CFR/USP-compliant method for sterility testing of cell-therapy products

H M Khuu [1], F Stock, M McGann, C S Carter, J W Atkins, P R Murray, E J Read

2006

Comparative Study > Transfusion. 2006 Dec;46(12):2071-82.
doi: 10.1111/j.1537-2995.2006.01041.x.

Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR-compliant method

Hanh M Khuu [1], Nayana Patel, Charles S Carter, Patrick R Murray, Elizabeth J Read

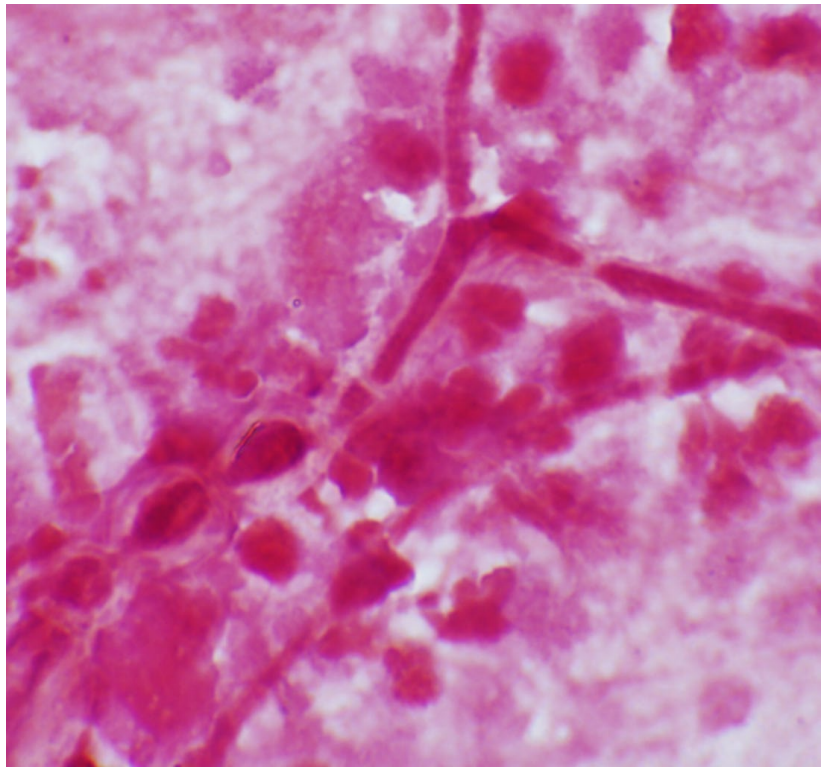
First Contamination Event (2015)

- April 2015
  - Two albumin vials found grossly contaminated with *Cladosporium* spp. and *Aspergillus nidulans*
  - FDA for-cause inspection.
  - Form 483, observations.
  - Hospital pharmacy was shut down.

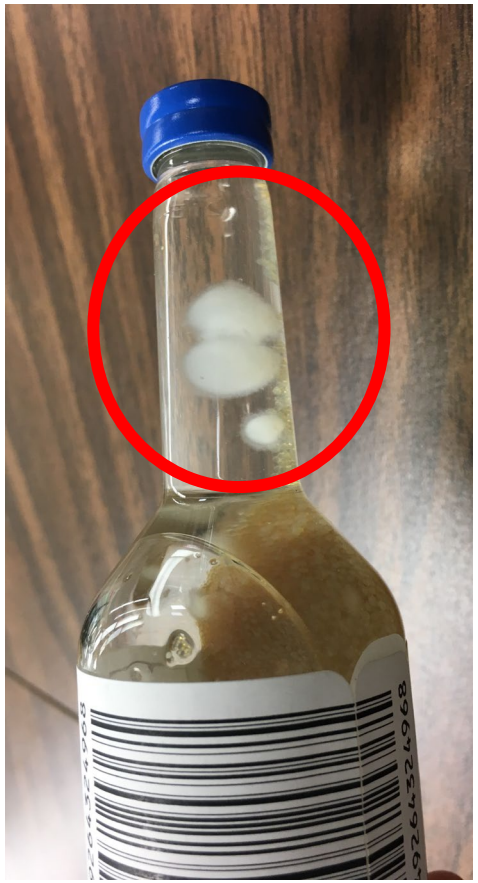
Published: 05 June 2015

Second Contamination Event (2015)

- Mold observed in NK cell product on final release testing Gram stain



- BACTEC failed to detect gross growth of mold in the bottles
- Multiple bottles collected during “in-process” testing were positive
- *Aspergillus terreus*



Red Team Report (2015 – 2016)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE
Mortality in Puerto Rico after Hurricane Maria

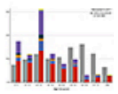
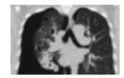


IMAGE CHALLENGE
What is the diagnosis?



PERSPECTIVE
Preserving Access f
with Disabilities

Perspective

Safety Lessons from the NIH Clinical Center

Tejal K. Gandhi, M.D., M.P.H., C.P.P.S.

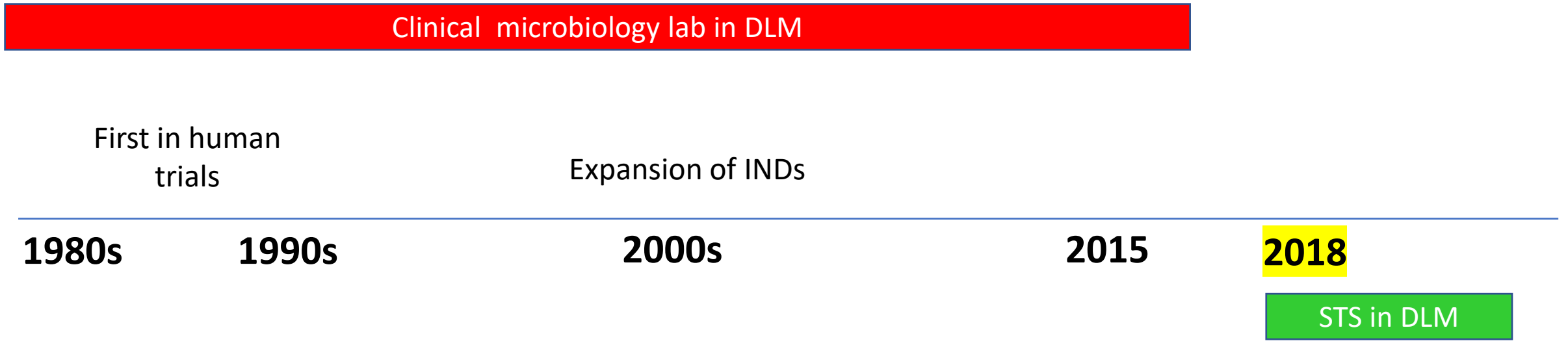
Article Metrics

5 References

The National Institutes of Health Clinical Center (NIHCC) has a long and storied list of accomplishments. Many practices begun at the NIHCC on the basis of NIH research have become the standard of care worldwide, and in many ways, it's a hospital like no other. Like other hospitals, however, it is susceptible to competing priorities that can lead to lapses that compromise patient safety. Recent events at the center provide important lessons for health professionals and leaders everywhere.

2016 Nov 3;375(18):1705-1707

Creation of the Sterility Testing Service



- Creating brand-new GMP testing lab (core microbiology lab to support for IRP), systems, operations, facilities, personnel from scratch.
- Challenge – to maintain operations during build out.

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

2019

Comprehensive Evaluation of Compendial USP<71>, BacT/Alert Dual-T, and Bactec FX for Detection of Product Sterility Testing Contaminants

Matthew R. England,[a] Frida Stock,[a] James E. T. Gebo,[a] Karen M. Frank,[a] Anna F. Lau[a]

[a]Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

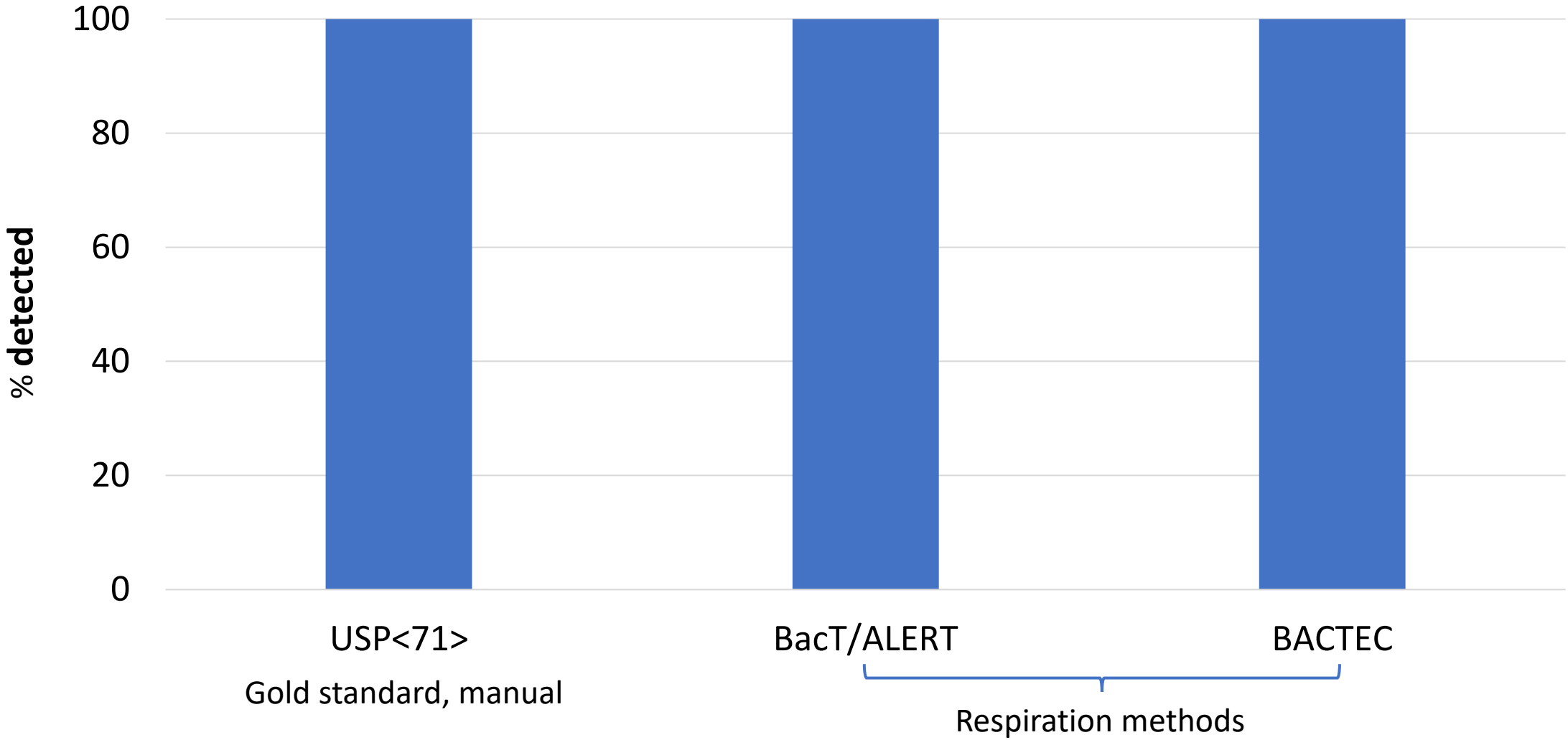
- Larger and diverse organism challenge set (n=118)
- 7 system comparison
- Current technology and media formulations

Matthew England, Ph.D., D(ABMM)

Frida Stock

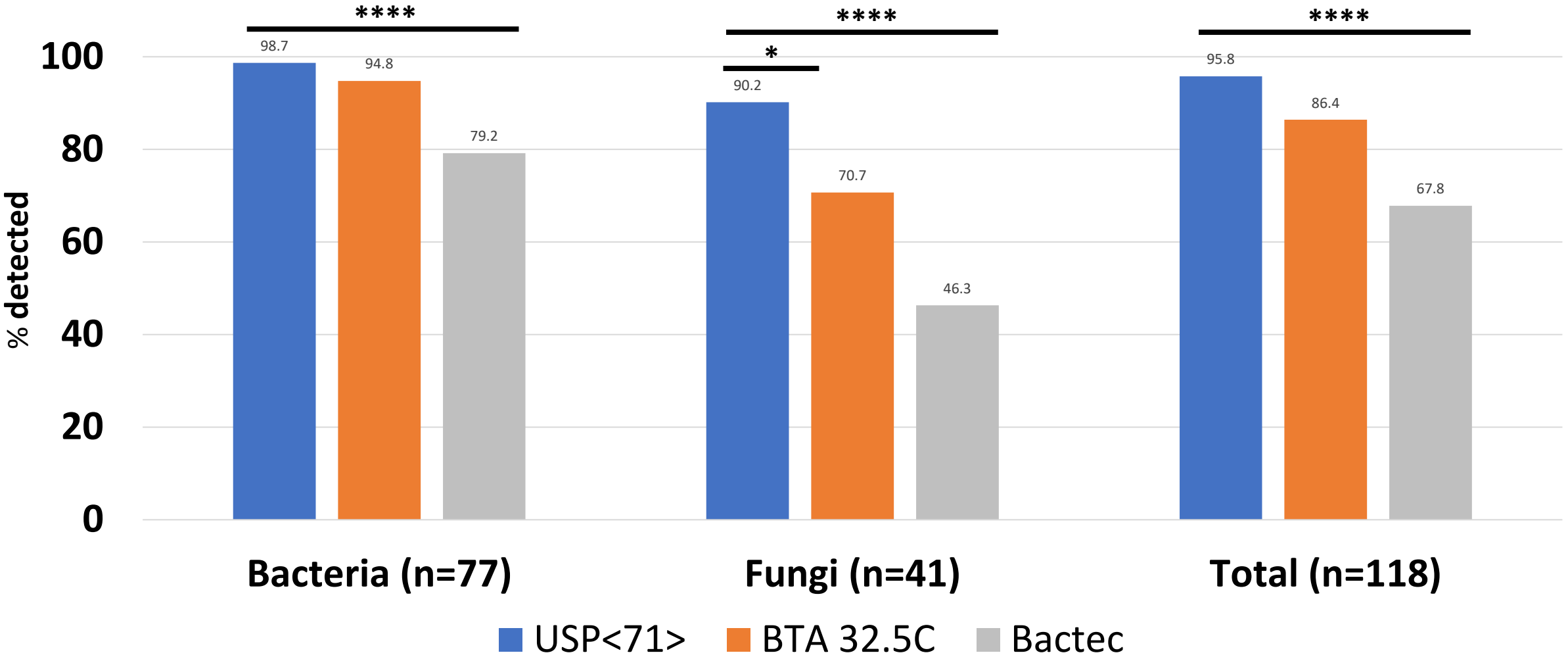
Equivalent Performance when Testing the 6 USP<71> Organisms

Matthew England, Ph.D.

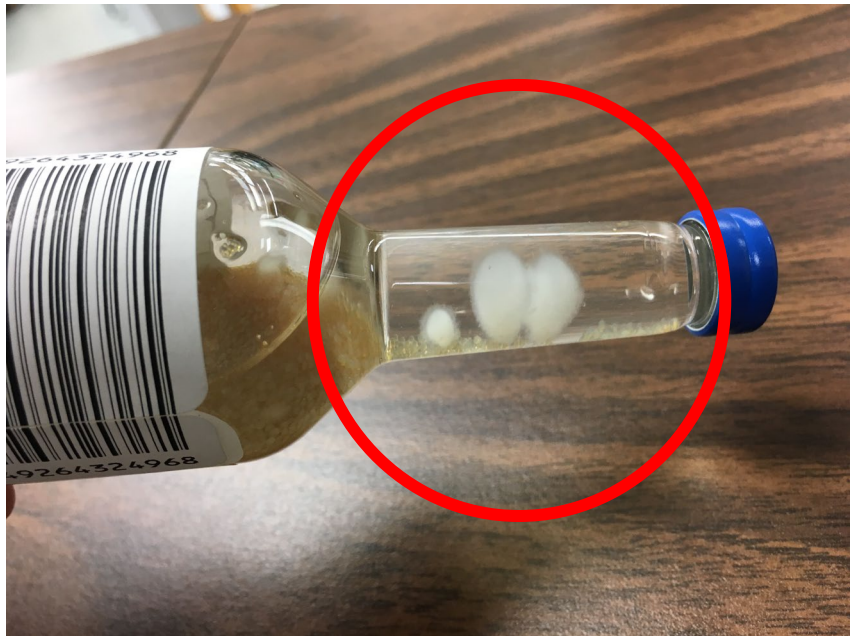


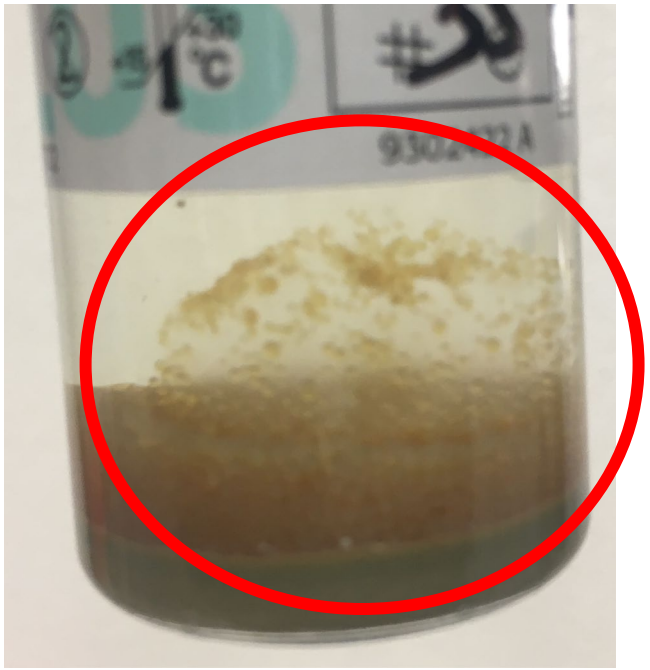
Expand organism test set (n=118) and extended incubation to 14 days

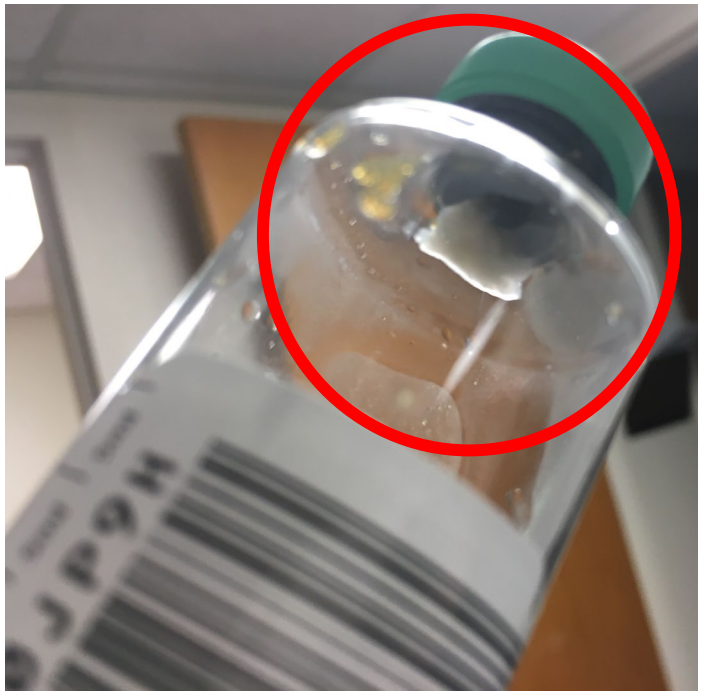
Matthew England, Ph.D.

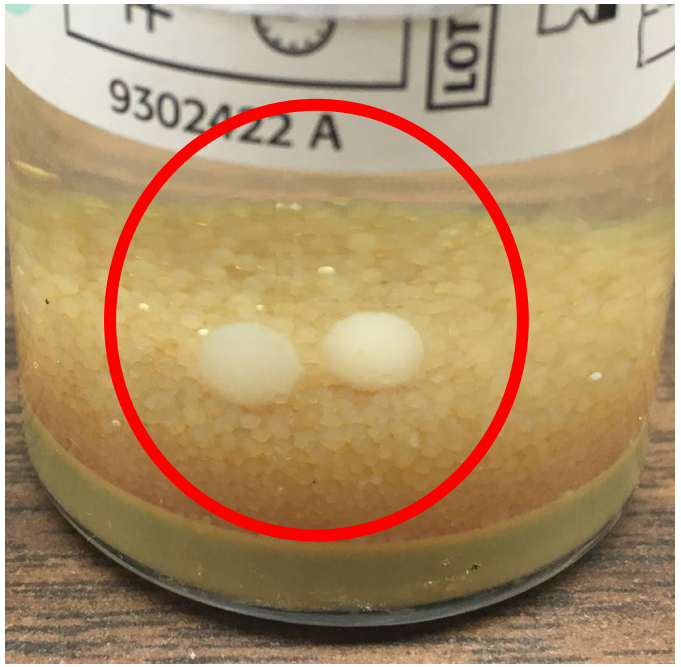


England et al, J. Clin. Microbiol. (2019)





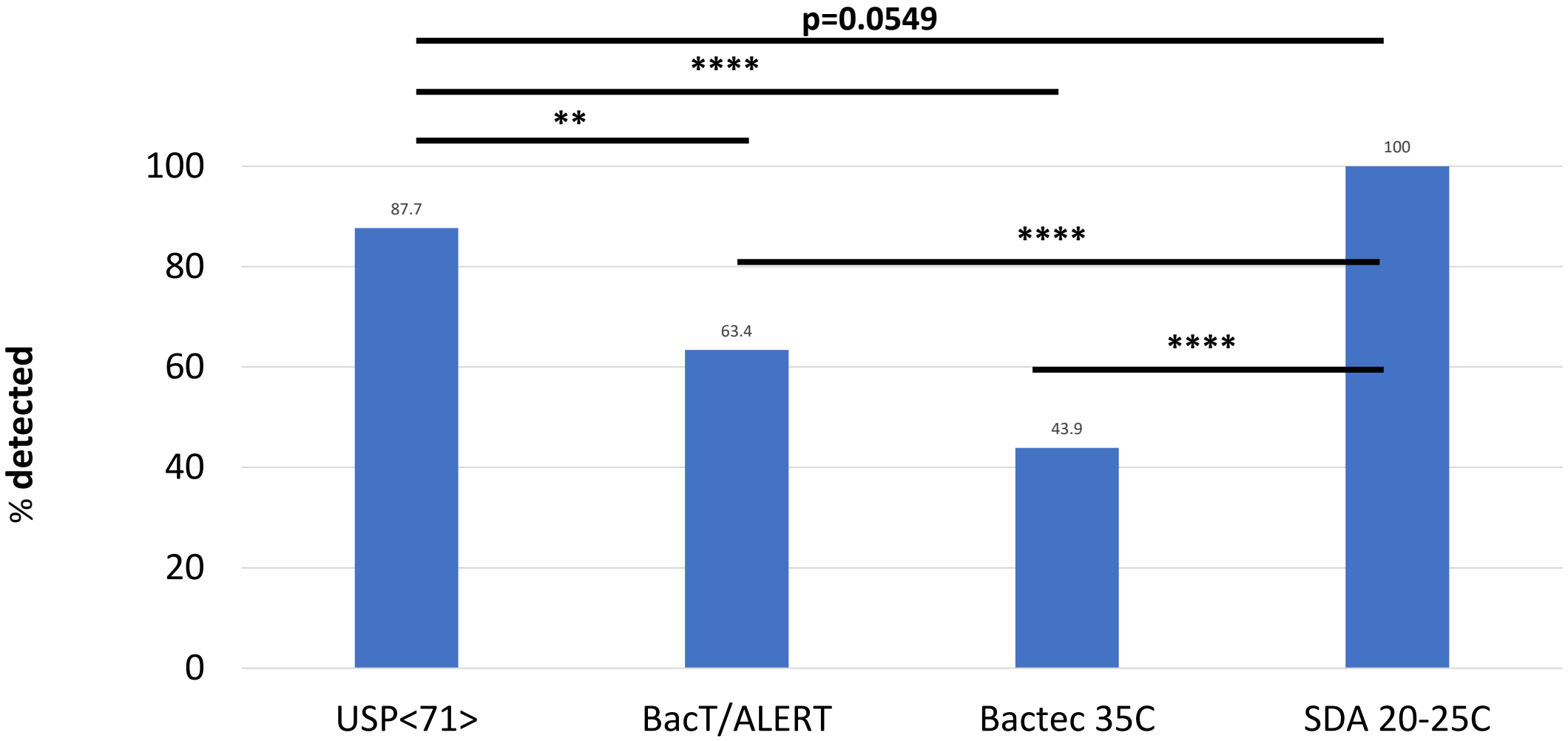




System did NOT detect gross contamination

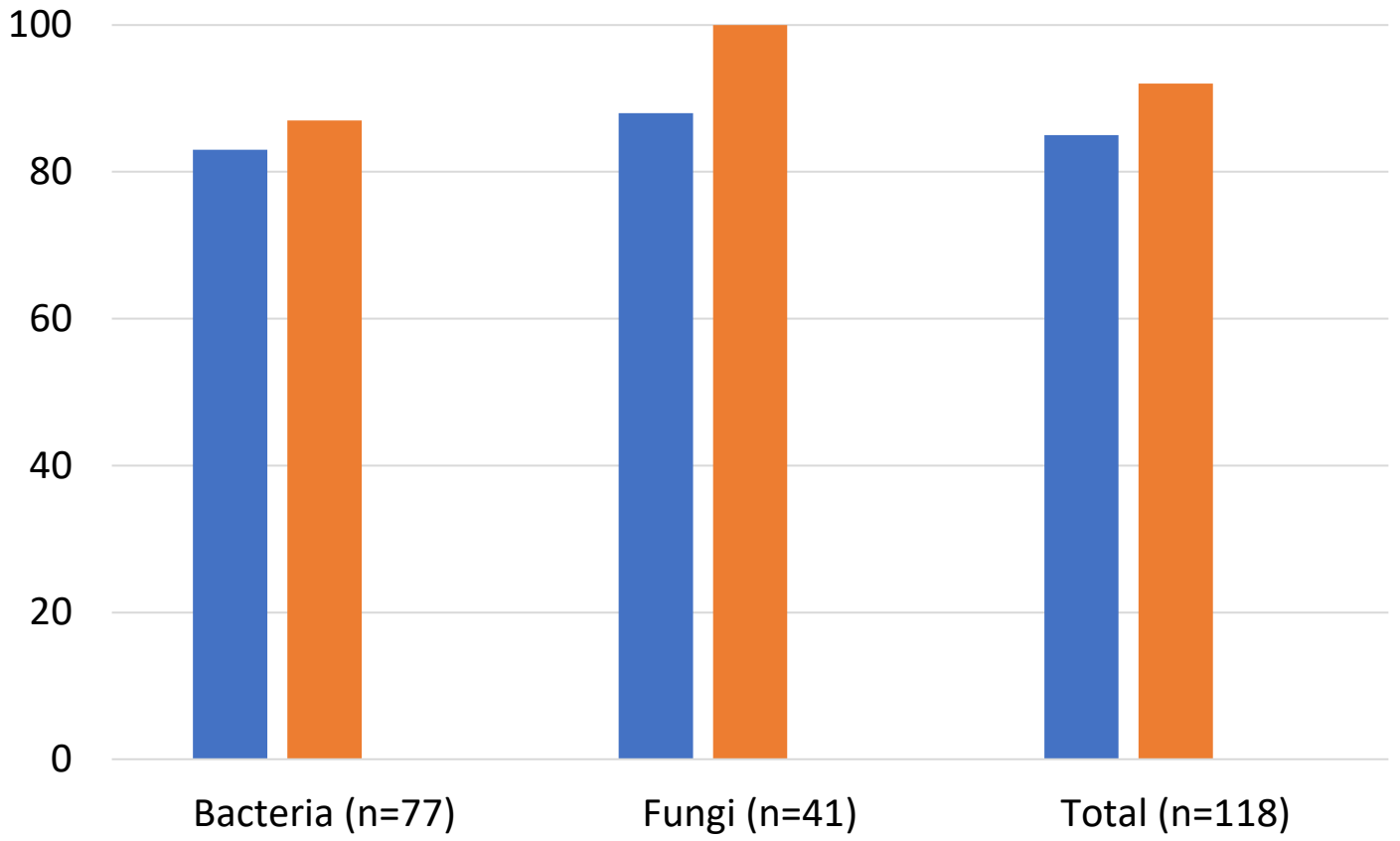
Culture on SDA Improves Fungal Detection (n=41)

Matthew England, Ph.D.



Revamp Sterility Testing Program at NIH

Matthew England, Ph.D.



USP<71>

BTA+SDA
(NIH Alternative method, starting 2019)

BacT/ALERT iFA+ and iFN+ bottles (32.5°C) with SDA culture (22.5°C)

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

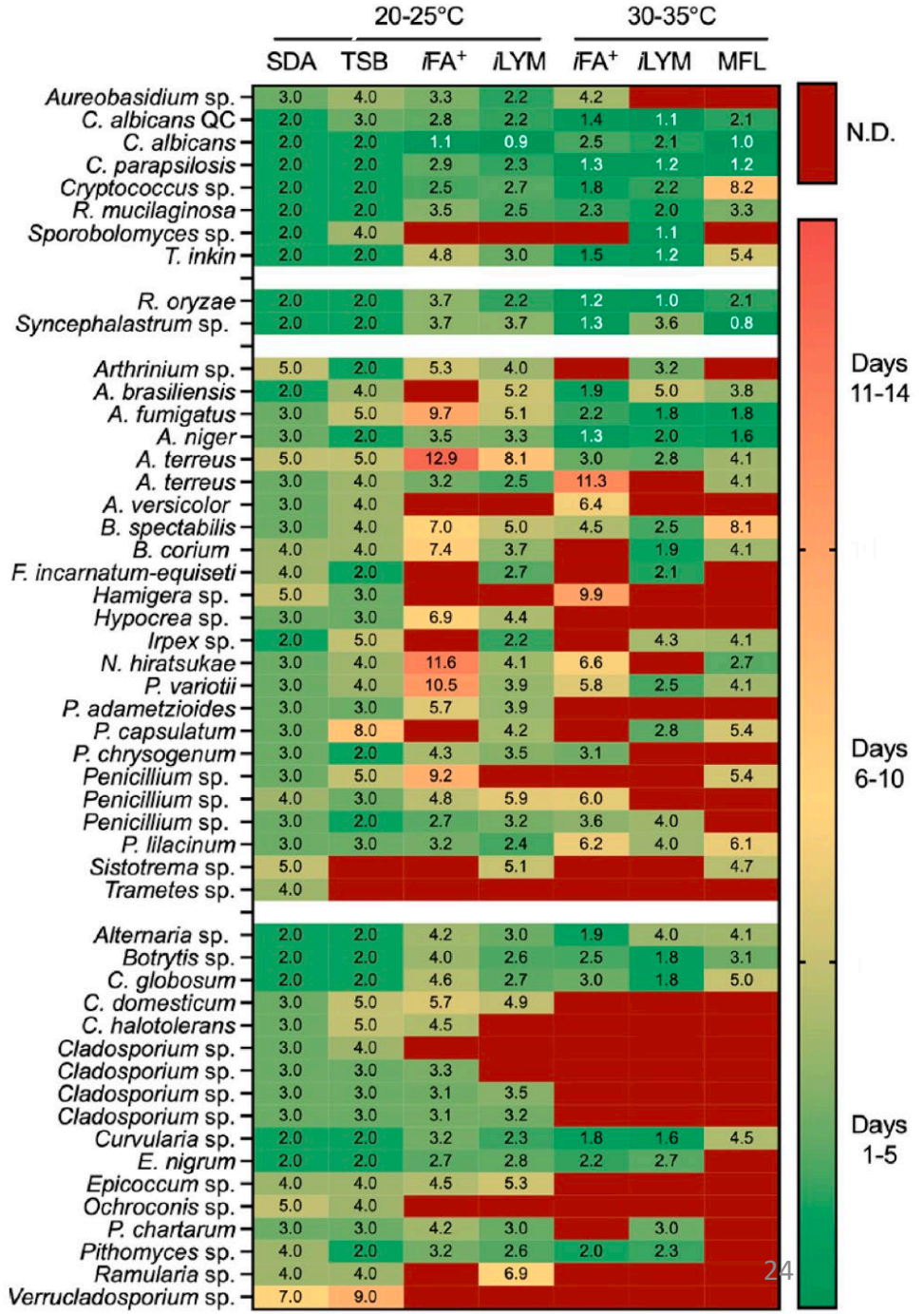
2021

Comprehensive Study Identifies a Sensitive, Low-Risk, Closed-System Model for Detection of Fungal Contaminants in Cell and Gene Therapy Products

Nicole E. Putnam,[a] Anna F. Lau[b]

Nicole Putnam, Ph.D., D(ABMM)

*i*LYM: Lactic Acid, Yeast, Mold



This is becoming an increasingly common request in clinical laboratories

American Society for Microbiology listservs

From: [redacted]
Date: Friday, January 14, 2022 at 10:25 AM
To: Lau, Anna (NIH/CC/DLM) [E] <anna.lau@nih.gov>
Subject: [EXTERNAL] Help Needed

- There is a surgeon here who undertaking an islet cell transplant program. Apparently they remove the patient own islet cells, treat them, and then put them back in the patient.
- The surgeon wants us to do sterility testing.
  - Is this ok if we are not FDA-cleared for donor testing?
  - What regulations would apply and what conditions for culture.

Sterility testing of Cell Therapy products 2019-02-08 14:18:00

Click here to view in a new browser window

Netters,

For those of you who have Cell Therapy/Stem Cell at your facility, would you please assist us with the following questions?
We are in the process of replacing our current blood culture analyzer with a newer version (BacT/Alert to Virtuo) and the bottles that Cell Therapy wants to use cannot be used on the Virtuo.

1. Does your Microbiology lab perform the sterility testing on the products?
2. If so, what analyzer and bottles are used? If not, who performs the sterility testing?
3. How many days are the cultures held?
4. Have you ever used an outside lab for this service? Pros/Cons?
5. Any other feedback regarding this?

From: [redacted]
Date: Thursday, January 13, 2022 at 3:14 PM
To: Lau, Anna (NIH/CC/DLM) [E] <anna.lau@nih.gov>
Subject: [EXTERNAL] Questions on cell sterility protocols

As we work on other non- COVID-19 projects one of them is a BMT program that will start in our system. One of the things that Micro has been asked to support the program with is cell sterility checks of harvested cells. The cells will not be manipulated but they will need to be checked prior to the infusions.

Why are Clinical Micro Lab asked to do Product Sterility Testing?

- Proximity of microbiology lab to manufacturing suites
- On-site microbiological expertise
- In-house testing more convenient (cost, result TAT)

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

2020

MINIREVIEW

Check for updates

Sterility Testing for Cellular Therapies: What Is the Role of the Clinical Microbiology Laboratory?

James E. T. Gebo,[a] Anna F. Lau[a]

[a]Sterility Testing Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA

2022

Clinical Microbiology Procedures Handbook, 4th Edition

Culture of Blood and Cellular Therapy Products in Blood Banking

WORLD MICROBE FORUM
20-24 JUNE 2021 | ONLINE WORLDWIDE
An ASM & FEMS Collaboration

2021

Cell Therapy and Pharmaceutical Microbiology Testing: What Clinical Micro Labs Need to Know

Session CPMH127 - Symposium

Clinical Microbiology NEWSLETTER

2021

CMN
Stay Current...
Stay Informed.

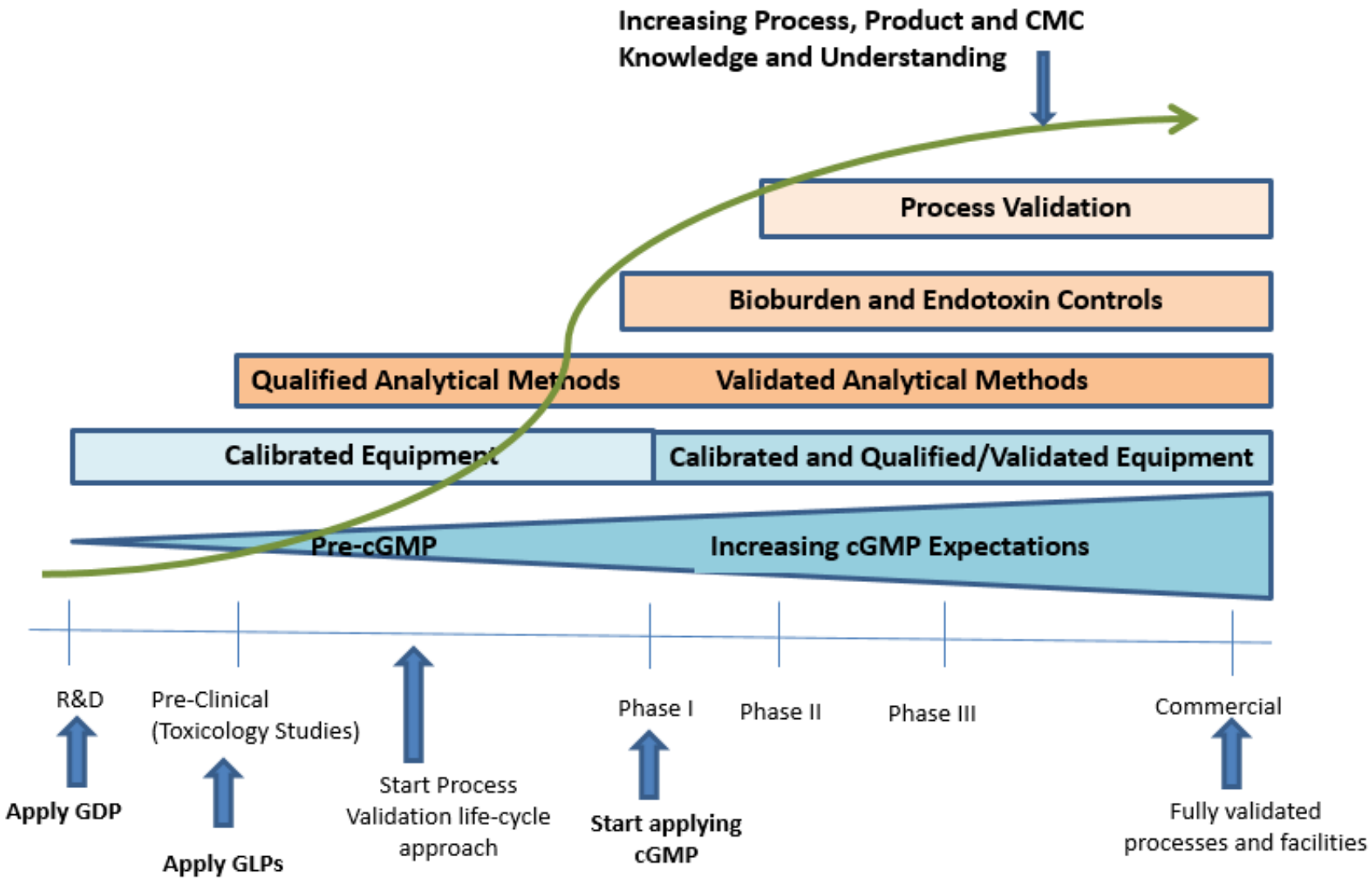
Vol. 43, No. 21
November 1, 2021
www.cmnewsletter.com

IN THIS ISSUE

A Side-by-Side Comparison of Clinical versus Current Good Manufacturing Practices (cGMP) Microbiology Laboratory Requirements for Sterility Testing of Cellular and Gene Therapy Products

James E.T. Gebo, B.S., M.P.A., Amanda D. East, M(ASCP), Anna F. Lau, Ph.D., D(ABMM), Sterility Testing Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland

Sliding Scale of GMP



PDA Technical Report 56

Workshop Questions/Comments

- “Risk assessment” - Risk is subjective
- Depends on expertise. Who is included in RA? You don’t know what you don’t know.
- Organisms recovered from facility → included in PQ and validation → depends on quality of the EM program (facility design, cleaning program, gowning program, materials management etc)
- Clinical industry has 510K cleared in vitro diagnostic tests (IVDs)
  - IVD risk is just as high
  - Can there be an equivalent for GMP? Vendor DMF with beta testing for XX product categories.
  - Clinical LDT (validation), Clinical IVD (verification) = requirements clearly defined by accrediting agencies.
- Better define the level of validation needed for phase I, II, III, commercial (not all can be USP<1223>)?
  - Is test PQ and product method suitability testing alone sufficient for early phase products?

NIH Sterility Testing Service