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

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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.
• 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)
<table>
<thead>
<tr>
<th>Cell &amp; Gene Therapy Products (n=24)</th>
<th>PET Radiolabeled Drugs (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-BCMA HC CAR-Transduced Autologous T Cells</td>
<td>BSS® Plus (BSS+) Media</td>
</tr>
<tr>
<td>Genetically Modified PBL Cell Therapies</td>
<td>CD33 CART Drug Product</td>
</tr>
<tr>
<td>Cryopreserved Cellular Products with and without Cryostor Rinse Off</td>
<td>Cryopreserved CD34, final product, post thaw bag, and post thaw vial</td>
</tr>
<tr>
<td>FGFR4 CAR-T Cells</td>
<td>Cell lysate in PBS</td>
</tr>
<tr>
<td>Induced pluripotent stem cells Retinal pigment epithelium</td>
<td>Red Blood Cells (Sickle Cell Vaccine)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Raw Materials (n=4)</th>
</tr>
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<tbody>
<tr>
<td>Infusion Bag Media</td>
</tr>
<tr>
<td>CryoStor CS10</td>
</tr>
<tr>
<td>Cryostar CS5 cryopreservative media containing 5% DMSO</td>
</tr>
<tr>
<td>200 Proof Ethyl Alcohol, Absolute (Dehydrated)</td>
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</tbody>
</table>

| Viral Vector (n=5) |
# Long History of Sterility Testing at the NIH

**Clinical microbiology lab in DLM**

<table>
<thead>
<tr>
<th>1980s</th>
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<th>2000s</th>
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<tr>
<td>Sterility testing in clinical micro USP&lt;71&gt;</td>
<td>Tedious, labor intensive, slow</td>
<td>New clin micro director switches to sterility testing using automated blood culture bottles</td>
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## 1980s
- Sterility testing in clinical micro USP<71>
- Tedious, labor intensive, slow

## 1990s
- **First in human trials**

## 2000s
- **Expansion of INDs**

### 1990s

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>1990</td>
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### 2000s

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

### 2004

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

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

### 2006

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

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

H M Khuu, 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
• Overall, significant faster time to positivity of respiration methods compared with USP<71>

Khuu et al (2004), Cytotherapy
Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR-compliant method

Hanh M Khuu, 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
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

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

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

Expansion of INDs

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

1980s 1990s 2000s

1980s 1990s 2000s

2004

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

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STOP
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.
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

Reducing Risk and Promoting Patient Safety for NIH Intramural Clinical Research

Draft Report

April, 2016

The Clinical Center Working Group Report to the Advisory Committee to the Director, NIH
Perspective

Safety Lessons from the NIH Clinical Center

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

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.
Creation of the Sterility Testing Service

First in human trials | Expansion of INDs

1980s | 1990s | 2000s | 2015 | 2018

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


*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
Equivalent Performance when Testing the 6 USP<71> Organisms

Matthew England, Ph.D.

Gold standard, manual

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

Matthew England, Ph.D.
System did NOT detect gross contamination
Culture on SDA Improves Fungal Detection (n=41)

Matthew England, Ph.D.

USP<71> BacT/ALERT Bactec 35C SDA 20-25C

\[ p = 0.0549 \]

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**

% detected

USP<71> 63.4 43.9 100

Bactec 35C 87.7 63.4 43.9

SDA 20-25C 100

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

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

iLYM: Lactic Acid, Yeast, Mold
This is becoming an increasingly common request in clinical laboratories

American Society for Microbiology listservs

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**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.

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

James E. T. Gebo,* Anna F. Lau*

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

Clinical Microbiology Procedures Handbook, 4th Edition

Culture of Blood and Cellular Therapy Products in Blood Banking

2021

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

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

Cell Therapy and Pharmaceutical Microbiology Testing: What Clinical Micro Labs Need to Know
Session CPMH127 - Symposium
Sliding Scale of GMP

Increasing Process, Product and CMC Knowledge and Understanding

Process Validation

Bioburden and Endotoxin Controls

Qualified Analytical Methods

Validated Analytical Methods

Calibrated Equipment

Calibrated and Qualified/Validated Equipment

Pre-cGMP

Increasing cGMP Expectations

R&D

Apply GDP

Apply GLPs

Pre-Clinical (Toxicology Studies)

Start Process Validation life-cycle approach

Phase I

Phase II

Phase III

Commercial

Fully validated processes and facilities

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