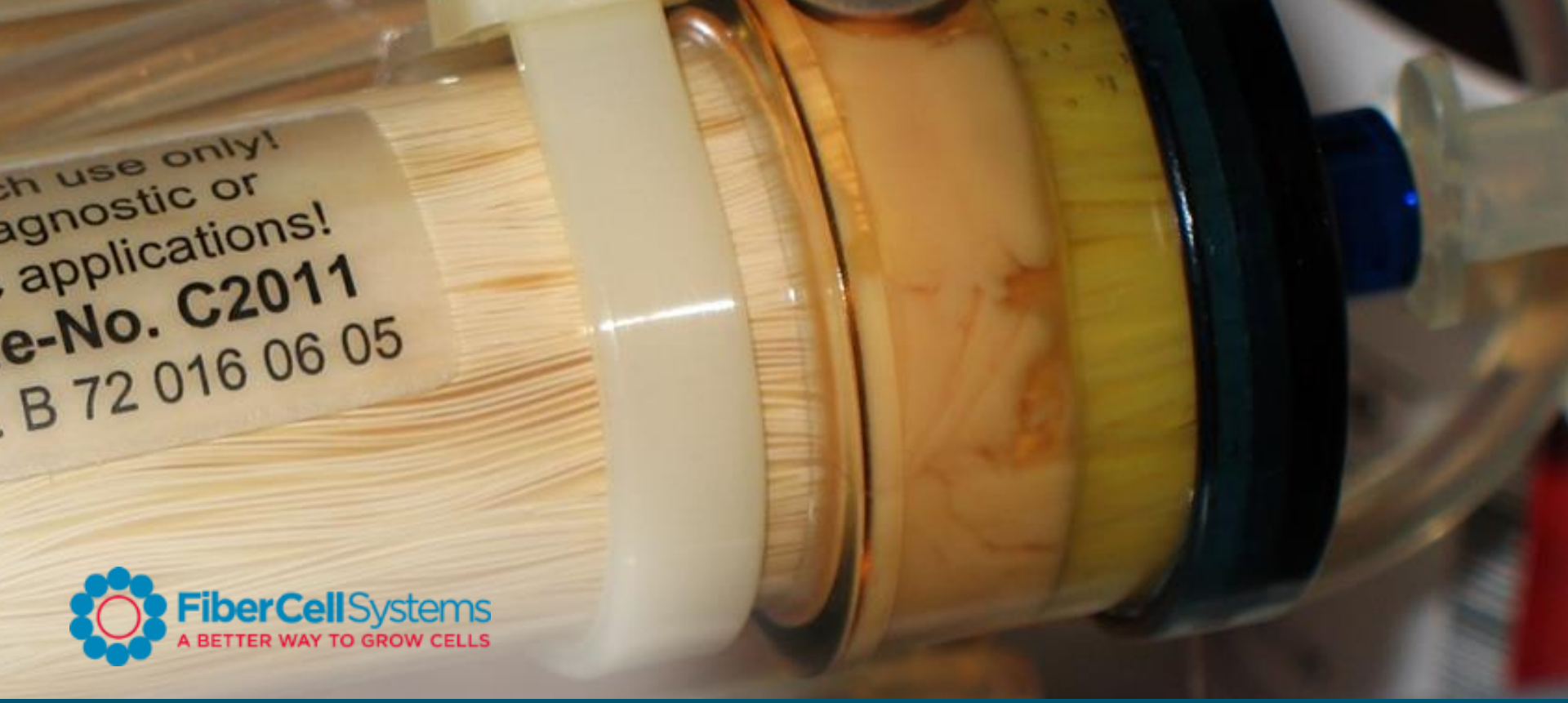
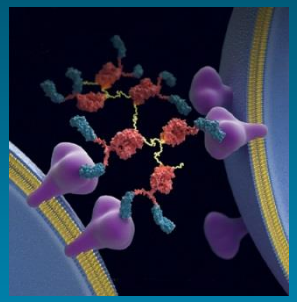



# Hollow Fiber Infection Model for Antibiotic PK/PD

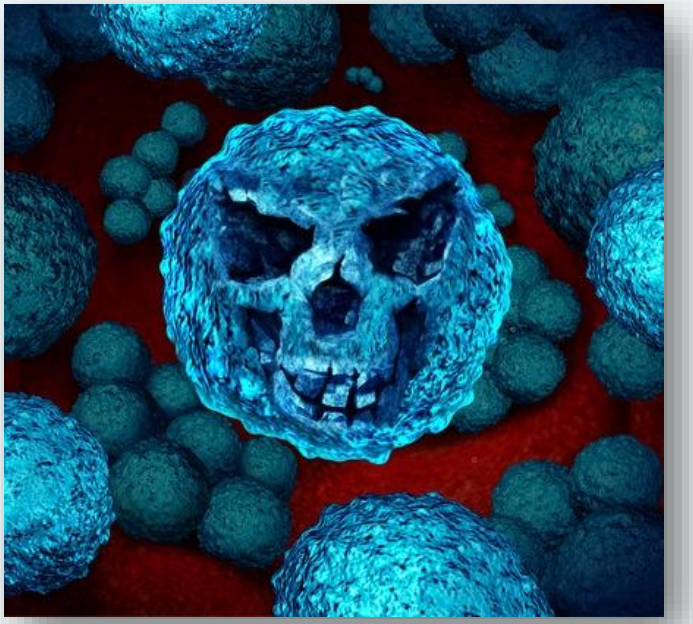


*By John J. S. Cadwell*

**www.fibercellsystems.com**

# Antibiotic Resistance

- Emerging antibiotic resistance is a major health concern
- 2 million people in the U.S. infected with antibiotic resistant bacteria last year
- 23,000 people died as a result of these infections, many more die from complications
- Most deaths related to antibiotic resistance occur in hospitals and nursing homes

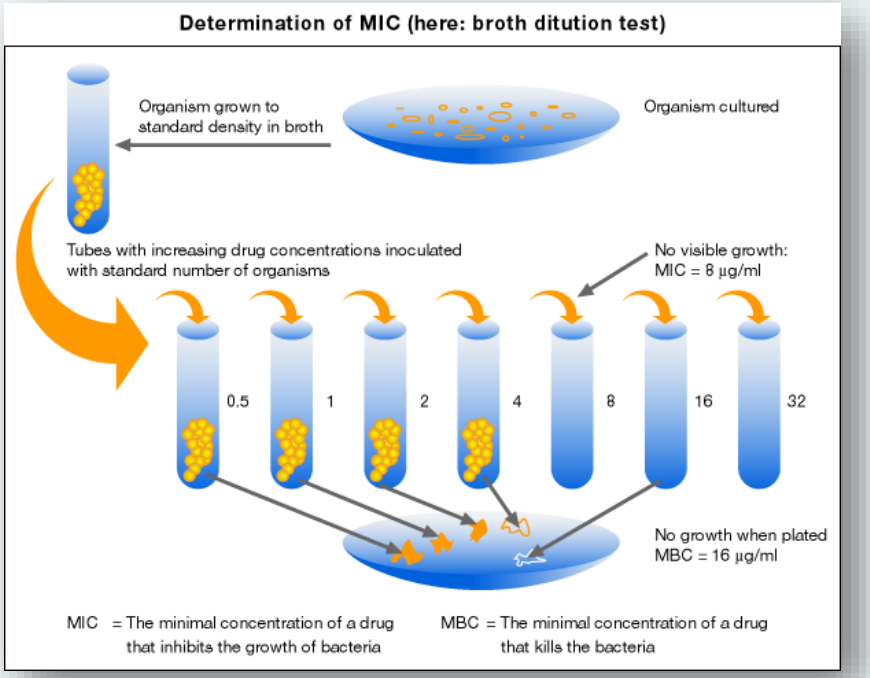


# Lack of New Antibiotics

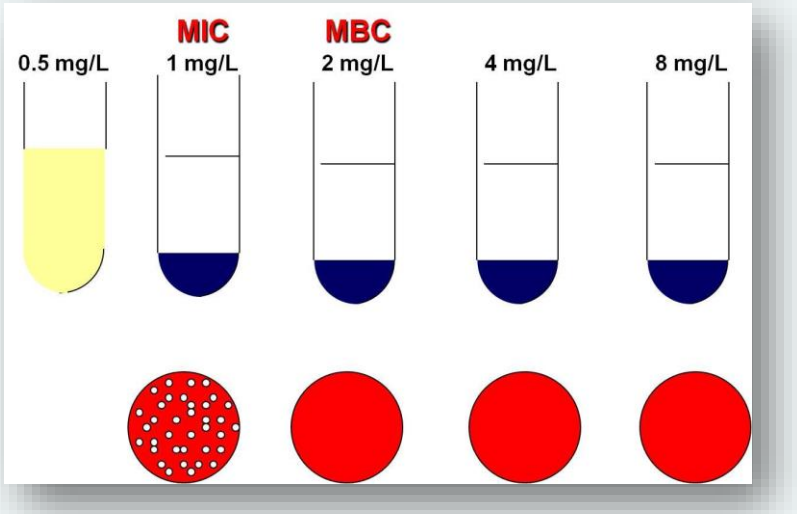
- Only 2 systemic antibiotic agents approved since 2008
- 16 approved between 1983 and 1987
- 3 reasons:
  - **Scientific:** Easy to discover antibiotics have already been found
  - **Economic:** Antibiotics represent a poor return on investment and new antibiotics reserved for difficult cases
  - **Regulatory:** FDA approval process increasingly complex and expensive.

# MIC: Minimum Inhibitory Concentration

- Lowest concentration of a drug that prevents a bacterial inoculum from growing to visibly detectable levels
- Time a drug concentration remains above the MIC
- Ratio of maximal drug concentration to MIC
- Ratio of the area under the concentration time curve to MIC

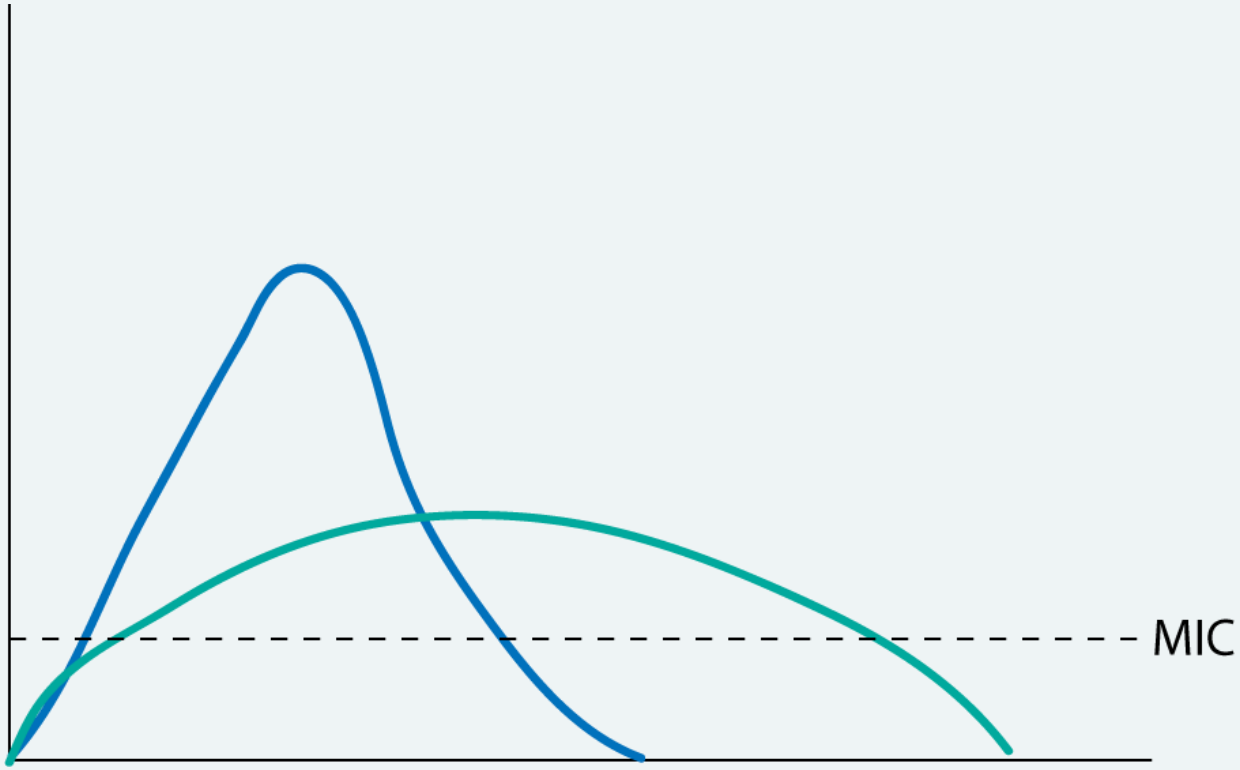


# MIC tells us nothing about:

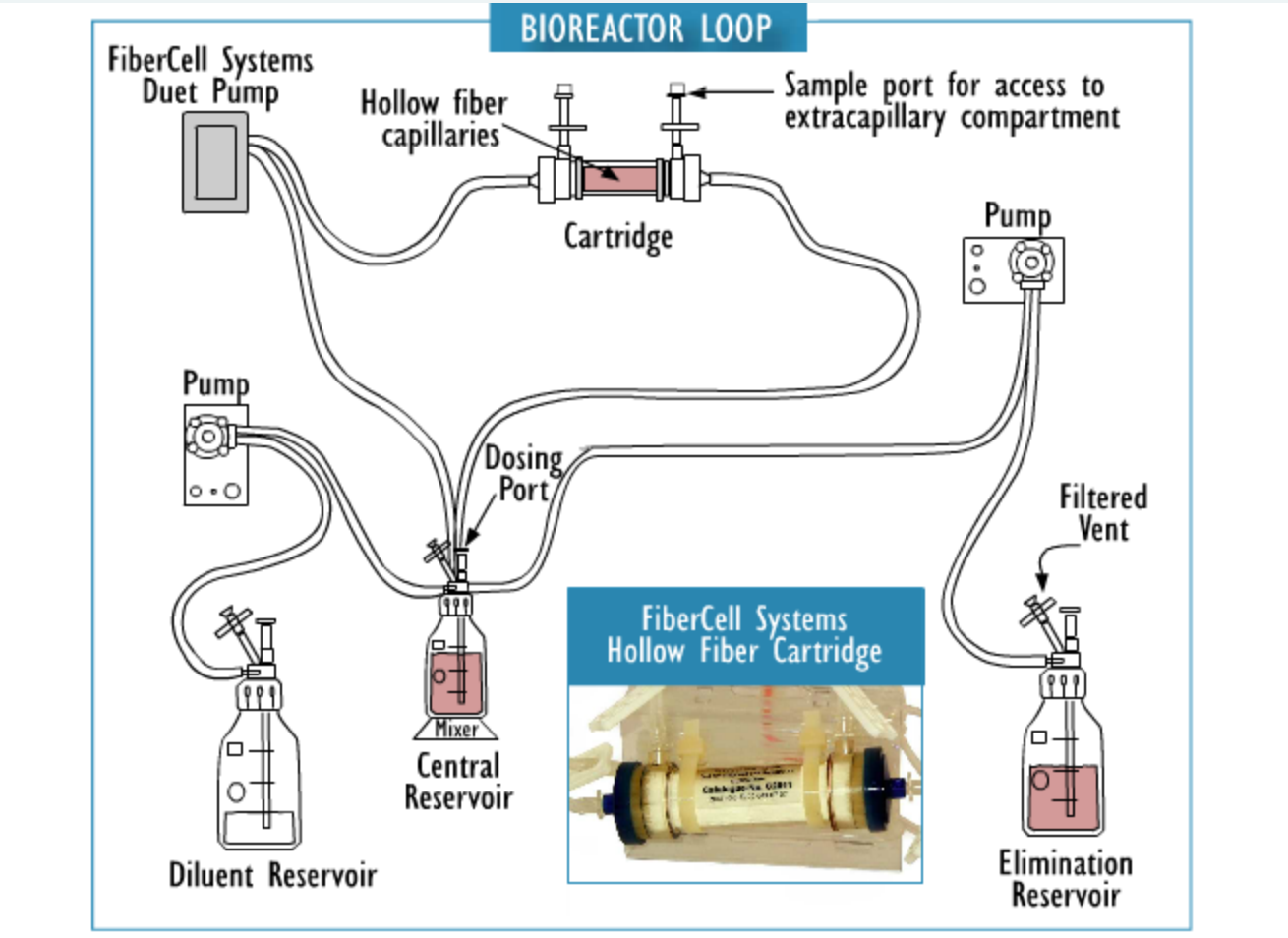



- Bacteriostatic or bactericidal
- Time or dosage dependent
- Rate of Bacterial killing
- Post-antibiotic effect
- Dosing profiles that prevent or facilitate resistance

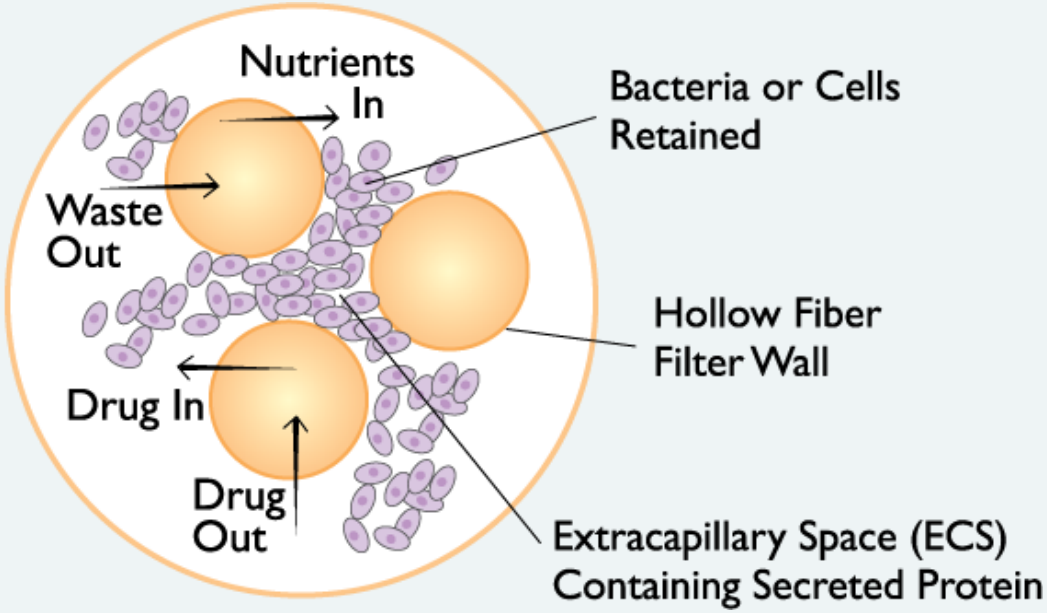
# Antibiotic efficacy is tied to both concentration and time.

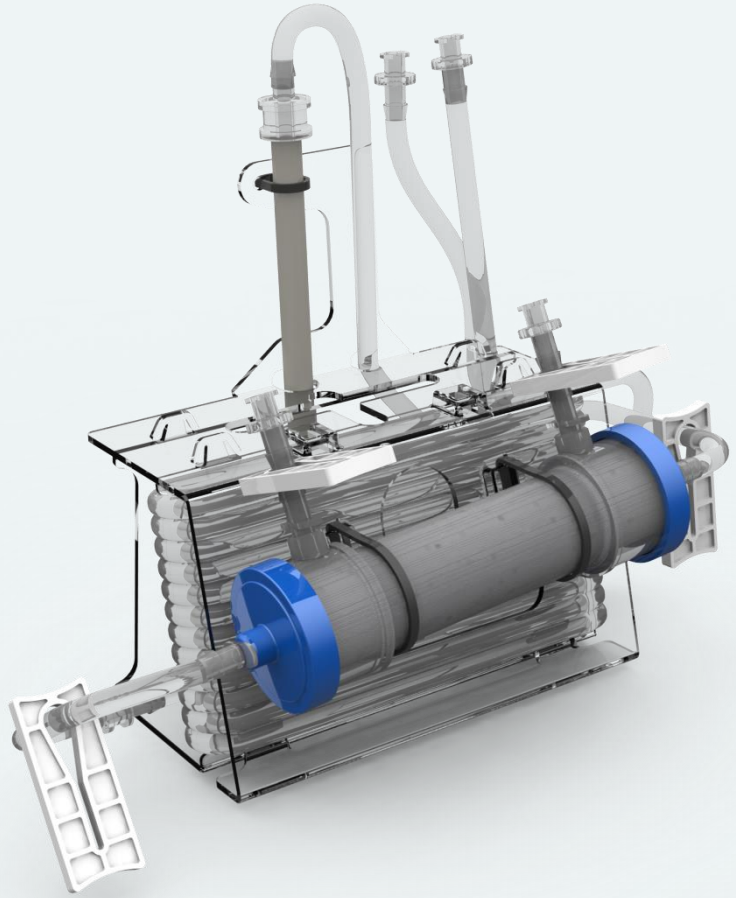


# Hollow Fiber Infection Model



# Hollow Fiber Cross-Section

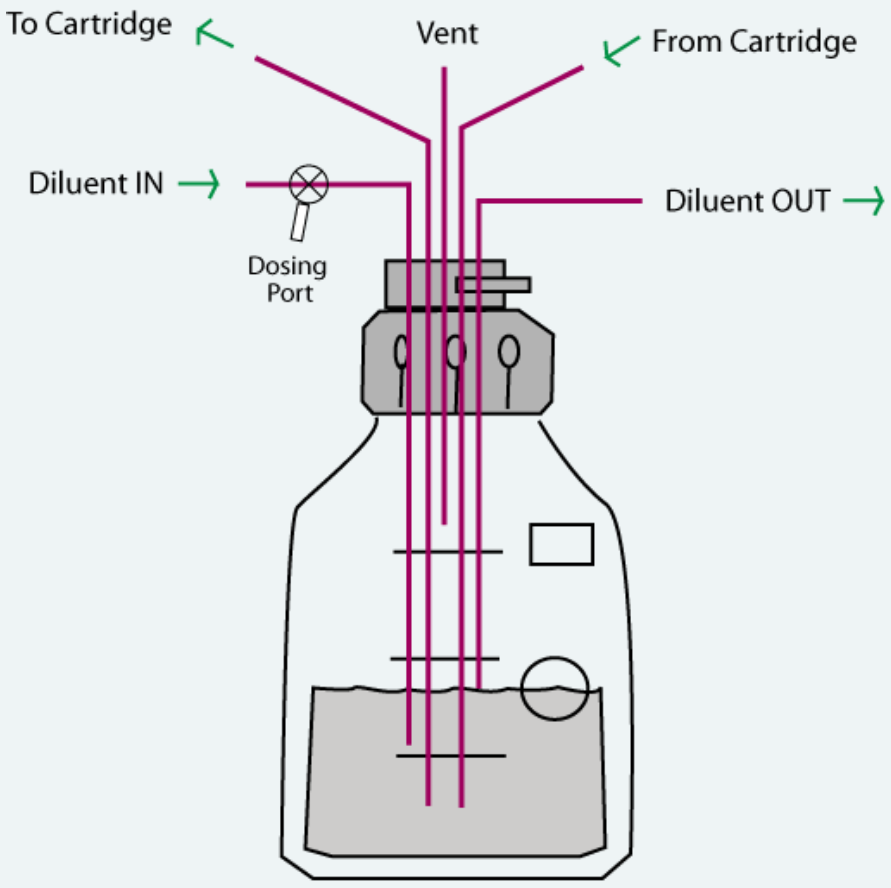




FiberCellSystems
A BETTER WAY TO GROW CELLS

www.fibercellsystems.com

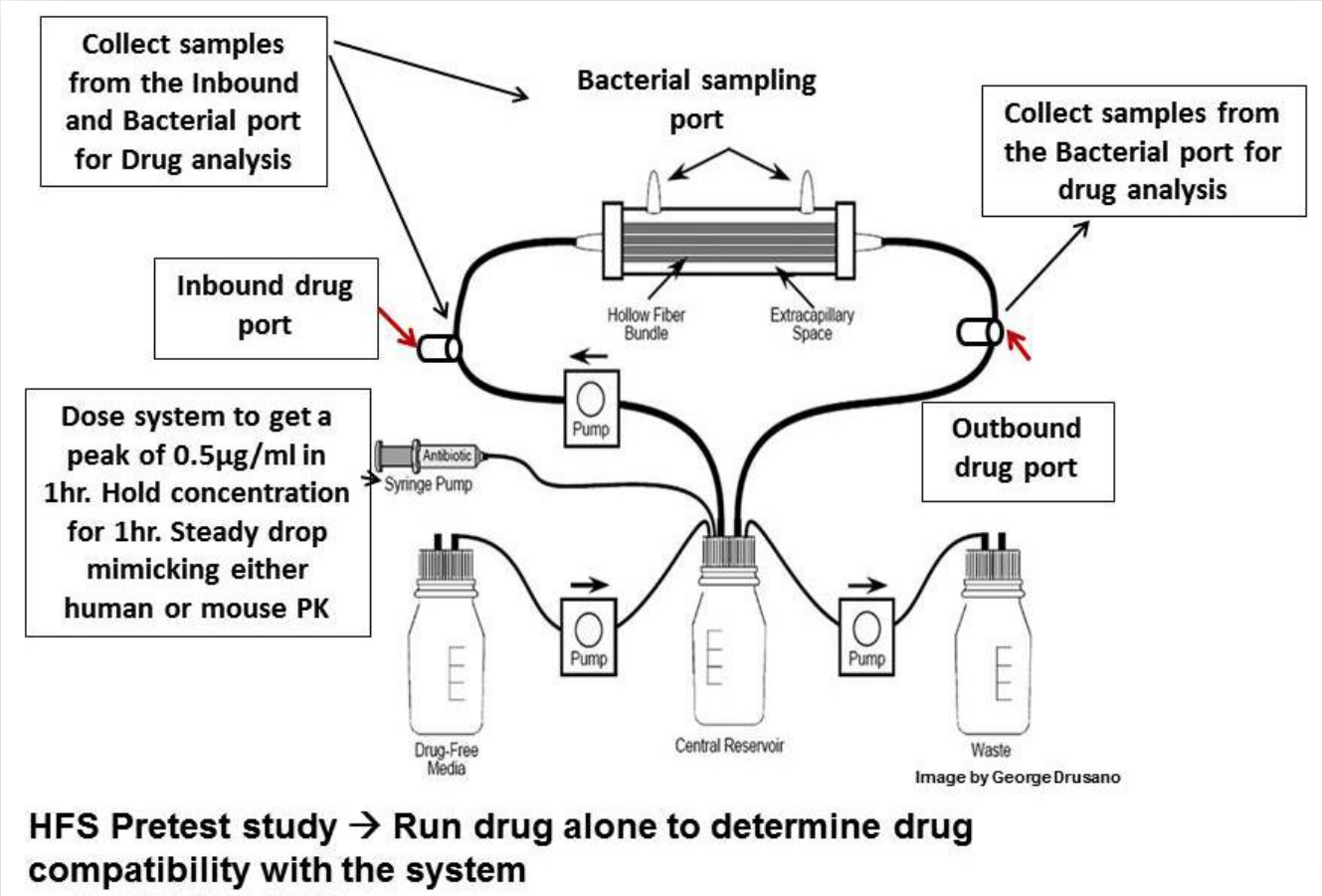
# Reservoir cap



# Advantages of the Hollow Fiber Infection Model

- Closed, bio-safe system
- Sampling over time
- Large number of organism can be tested, revealing resistance
- Precisely simulates human PK/PD
- Repetitive sampling over time, both drug and organism
- Total kill
- Single use, disposable, consistent
- Two drug models can be tested
- Can model both dosing curve and elimination curve
- Can look at bacteria in different growth phases and in combination with cells. Antiviral PK/PD as well.

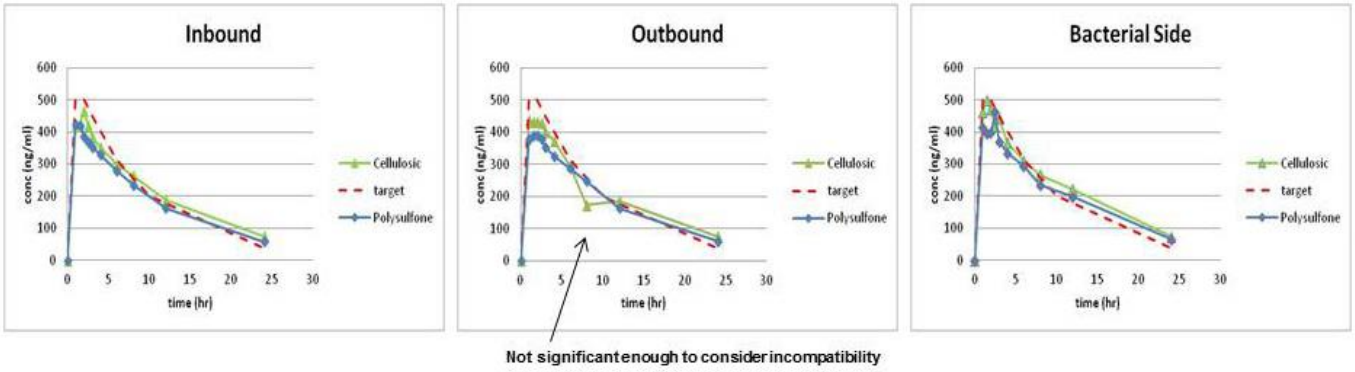
# Hollow Fiber Pretest Study Scheme

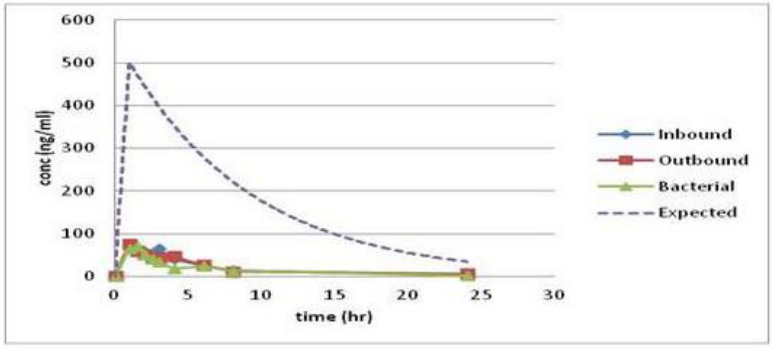



**HFS Pretest study → Run drug alone to determine drug compatibility with the system**

# PK Profile

**This drug showed good compatibility with both cartridges.**



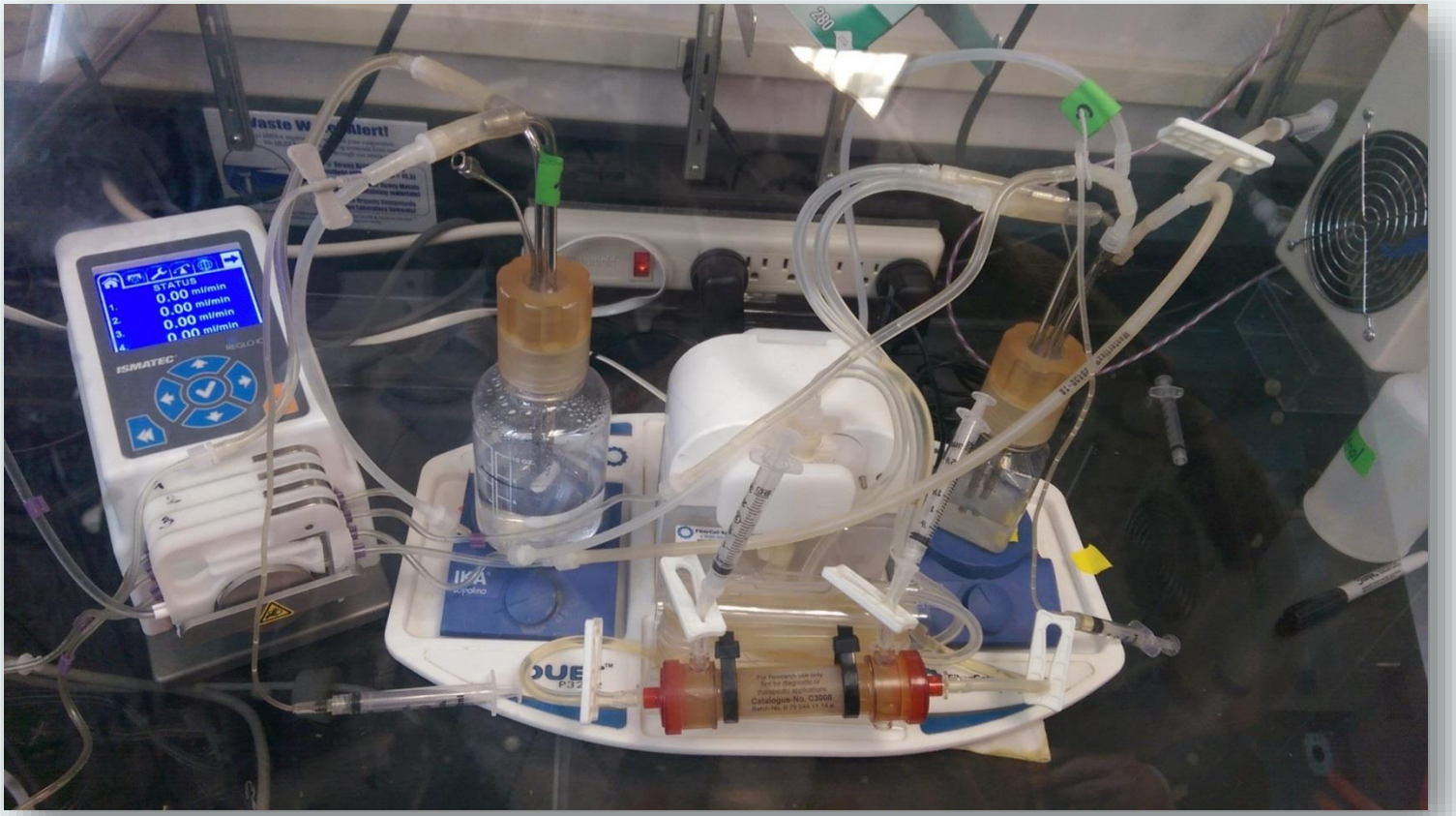




**This drug is not a good candidate for HFS use**

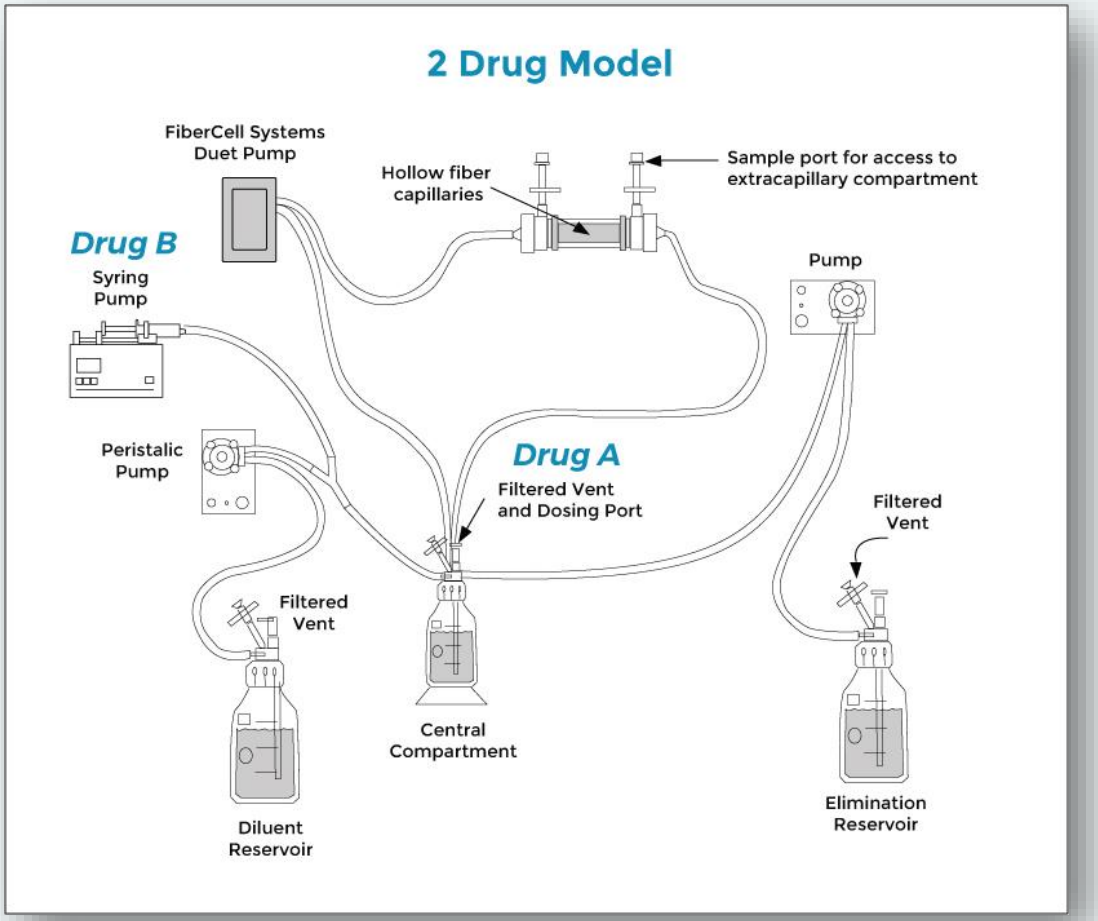

FiberCell Systems
A BETTER WAY TO GROW CELLS

www.fibercellsystems.com

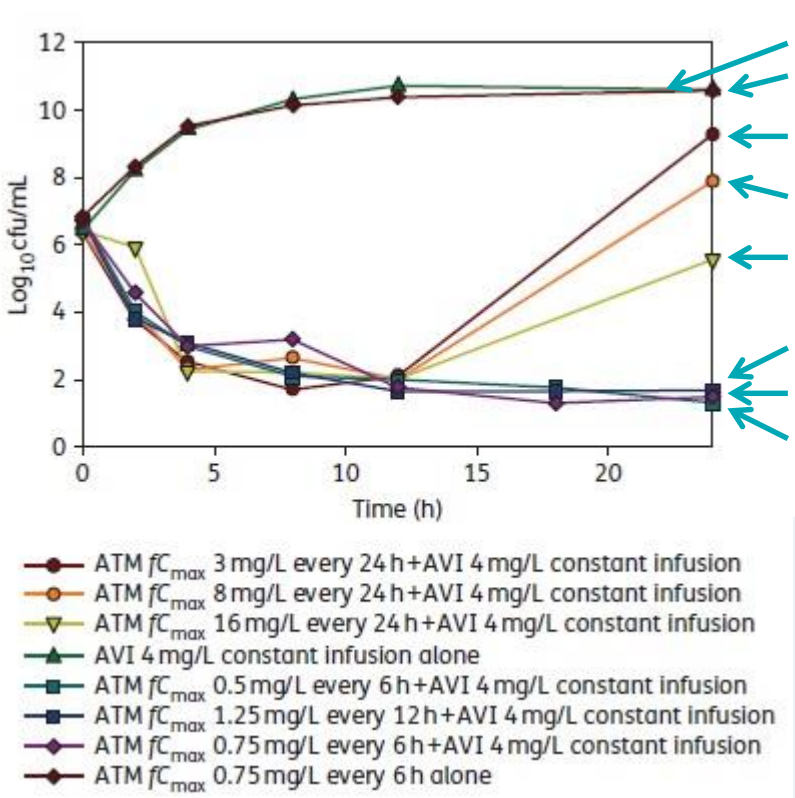
# Anaerobic Chamber



# Two Drug Model



# Drug Combination – Aztreonam/Avibactam




AVI 4 mg/L alone

ATM 0.75 mg/L-6 hrs alone

ATM 3 mg/L-24 hrs + AVI 4 mg/L

ATM 8 mg/L-24 hrs + AVI 4 mg/L

ATM 16 mg/L-24 hrs + AVI 4 mg/L

ATM 0.5 mg/L-6 hrs + AVI 4 mg/L

ATM 1.25 mg/L-12 hrs + AVI 4 mg/L

ATM 0.75 mg/L-6 hrs + AVI 4 mg/L

- Bacteria regrow after 4~8 hrs with once-daily dosing.
- When administered more frequently, total suppression was achieved at 24 hrs.

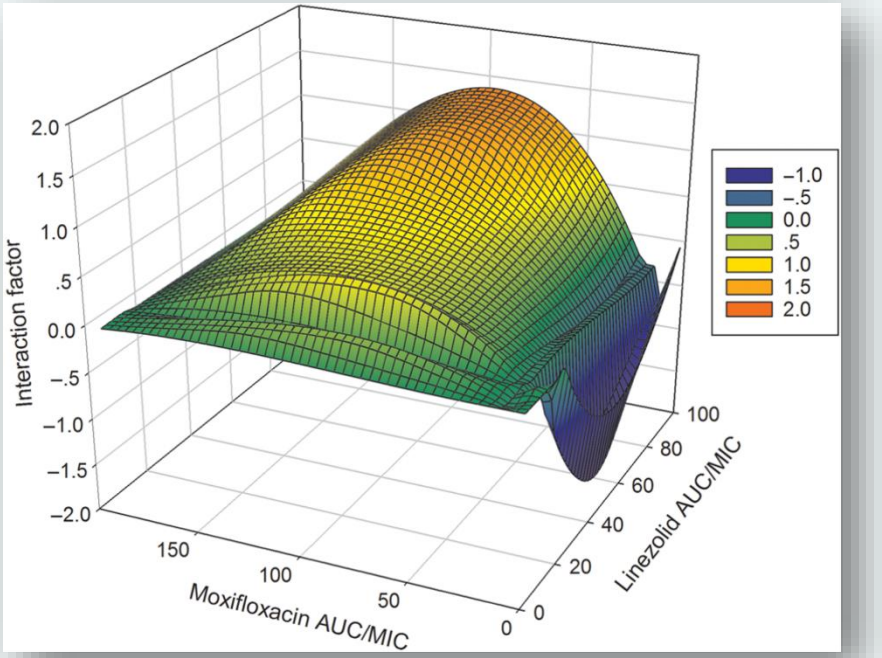
# Pediatric Therapy for TB

- Different bacillary burden
- Distribution of disease (not just in lungs)
- Drug metabolism and distribution
- Toxicity
- Adult regimen treatment for 18 months, more than 25% of children develop hearing loss

OXFORD
UNIVERSITY PRESS

From: **Concentration-Dependent Synergy and Antagonism of Linezolid and Moxifloxacin in the Treatment of Childhood Tuberculosis: The Dynamic Duo**

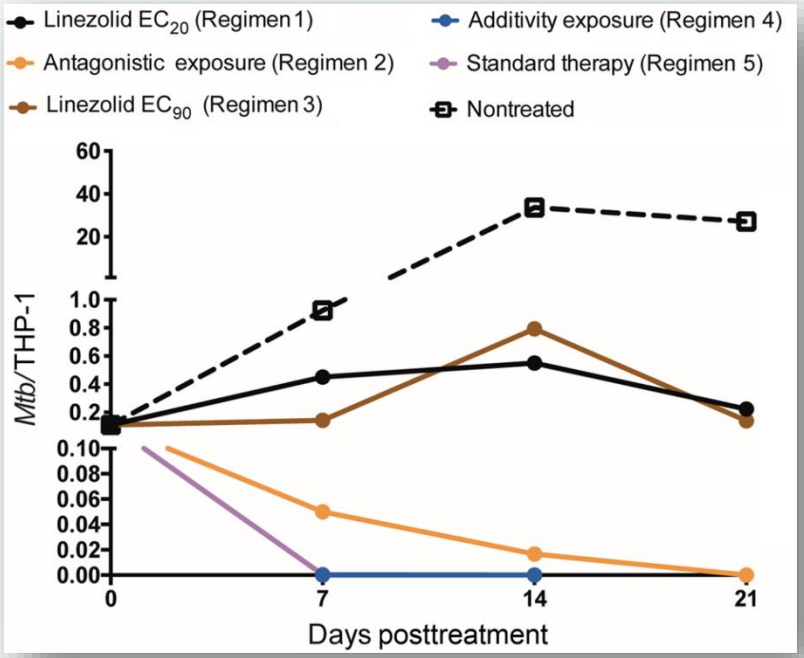
Exposure-response surface for the linezolid-moxifloxacin combination effect against intracellular Mycobacterium tuberculosis, in wells. The figure shows antagonism on the surface bounded by moxifloxacin 0- to 24-hour area under the curve ($AUC_{0–24}$)/minimum inhibitory concentration (MIC) ratios of 11.52–19.20 and linezolid $AUC_{0–24}$/MIC ratios of 12.0–22.08, shown in deep blue. The interaction factor was −0.02 (95% confidence interval [CI], −.03 to −.01). The zone of synergy was narrower, and was a ridge along a linezolid $AUC_{0–24}$/MIC ratio of 9.12 bounded by moxifloxacin $AUC_{0–24}$/MIC ratios of 19.2–192 with an interaction factor of 0.01 (95% CI, .01–.01). The rest of the surface, shown in shades of green, demonstrated additivity based on the finding that the observed effect minus the expected effect was zero.



OXFORD
UNIVERSITY PRESS

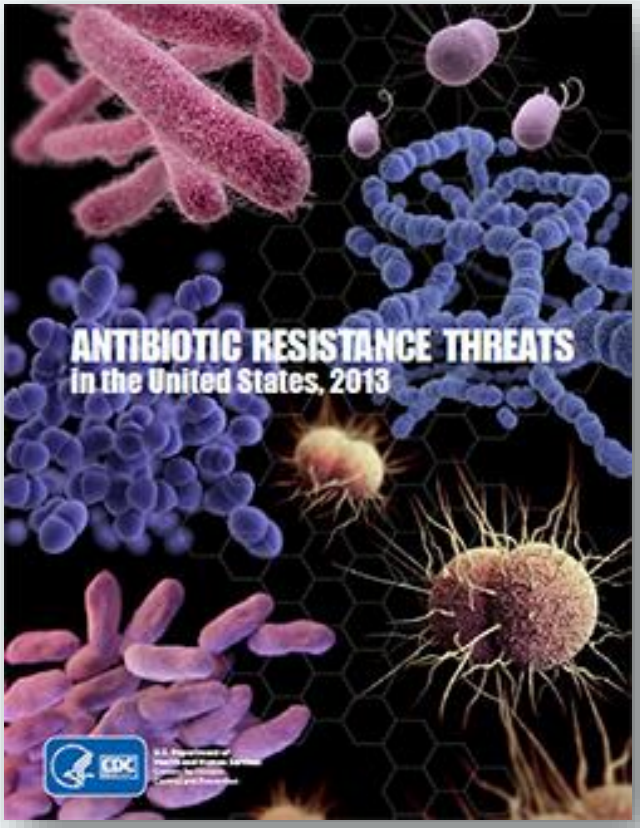
From: **Concentration-Dependent Synergy and Antagonism of Linezolid and Moxifloxacin in the Treatment of Childhood Tuberculosis: The Dynamic Duo**

Effect of microbial burden on THP-1 cells when expressed as a ratio of colony-forming units to number of THP-1 monocytes. Estimates are mean and standard deviation for 3 replicate hollow fiber systems. The number on bacteria per THP-1 cell is a composite of bacterial burden and drug toxicity–related viability of THP-1. The pattern and ranking order of regimens based on kill rates did not change, even when taking survival of THP-1 cells into account, and follows that of total bacterial burden shown in Figure . The slopes for the additivity exposure (regimen 4) and standard therapy regimen overlap completely, so that only one is visible in the figure. Abbreviations: $EC_{20}$, exposure associated with 20% of maximal kill; $EC_{90}$, exposure associated with 90% of maximal kill; Mtb, Mycobacterium tuberculosis.



# Regulatory position

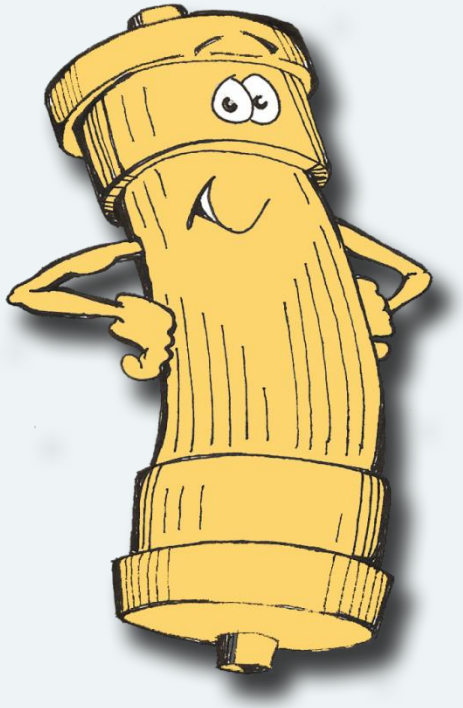
- EMA endorsement for TB
- FDA expected to follow suit
- Cartridges manufactured under ISO-14644-1 class 8



# The hollow fiber infection model is a complementary and additional tool for drug development, to be implemented at the earliest stages

- Optimal dose selection and route of administration
- Optimal dosing schedule
- Possible combination therapies
- Defines emerging resistance
- Defines total kill
- Post-approval drug regimen optimization
- Can support trial design for Phase I, II, III and IV clinical trials

Thank you.



FiberCell Systems
A BETTER WAY TO GROW CELLS

www.fibercellsystems.com