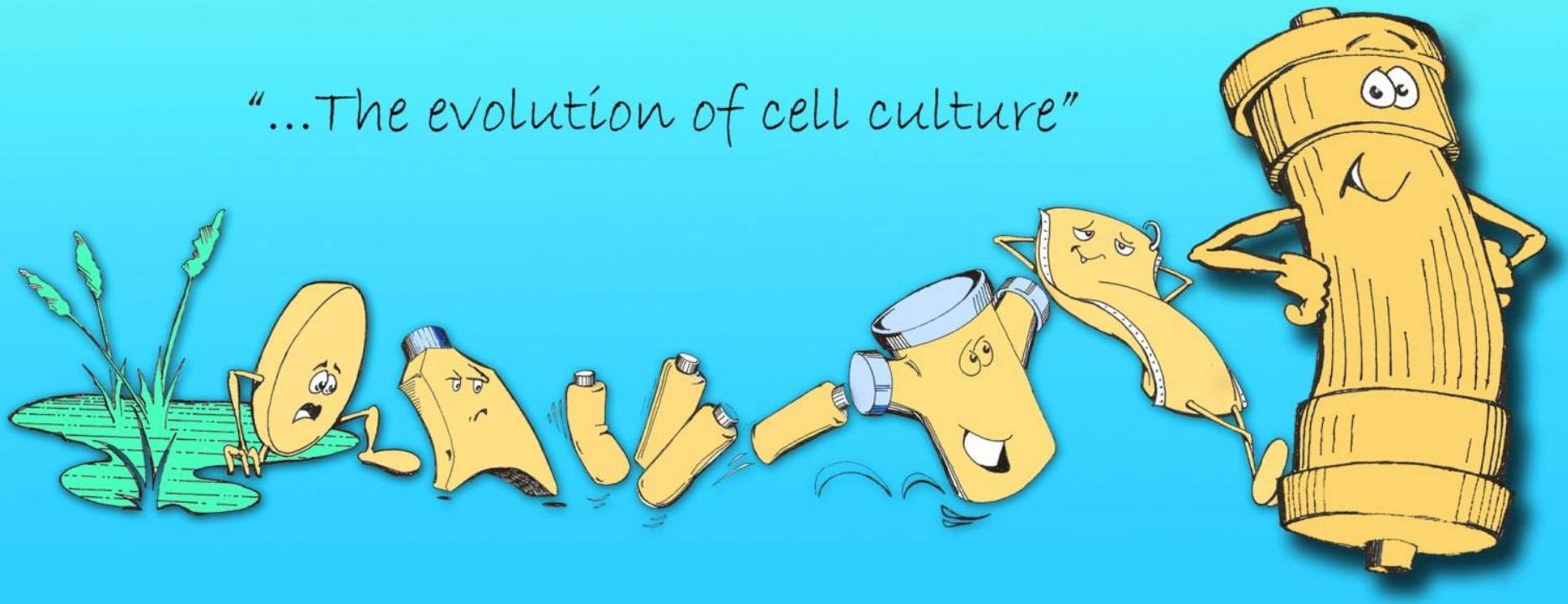


Hollow Fiber Infection Model for Antibiotic PK/PD

By John J.S. Cadwell

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"...The evolution of cell culture"



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.



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Lack of new antibiotics

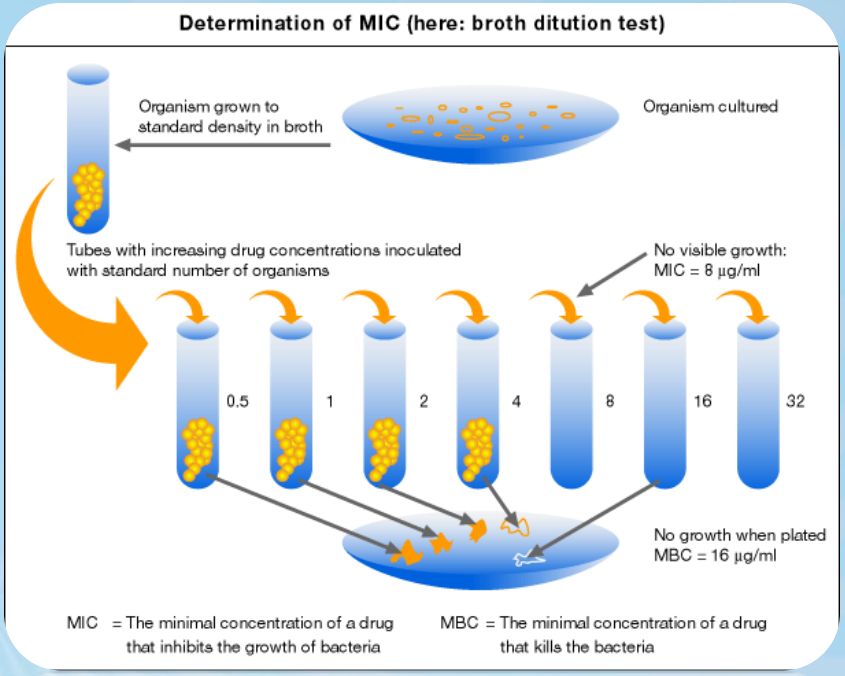


- Only 2 systemic antibiotic agents approved since 2008
- 16 approved between 1983 and 1987
- 3 reasons:
  - **Scientific:** Easy to discover antibiotics have already been found
  - **Economic:** Antibiotics represent a poor return on investment and new antibiotics reserved for difficult cases
  - **Regulatory:**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

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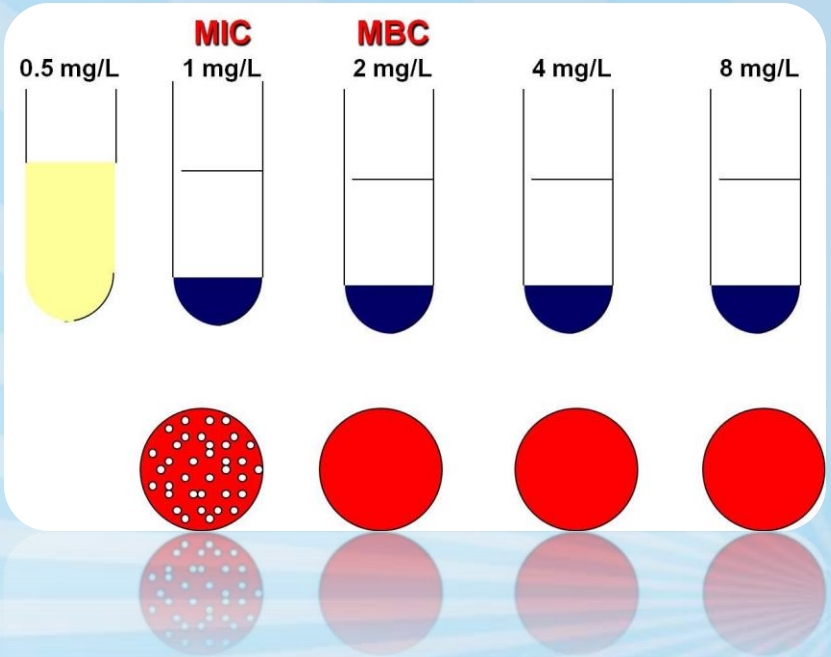
MIC: Minimum Inhibitory Concentration

- 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



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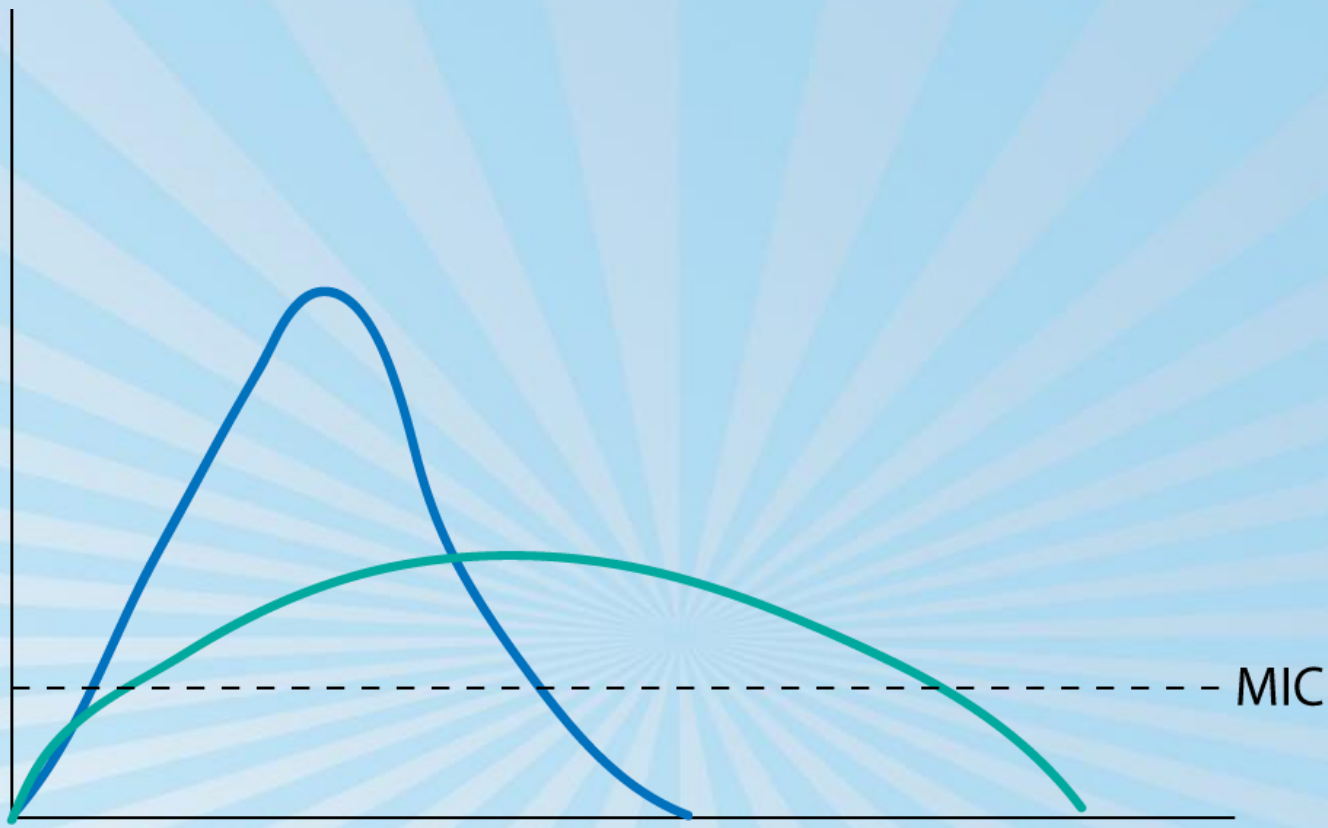
MIC tells us nothing about:



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

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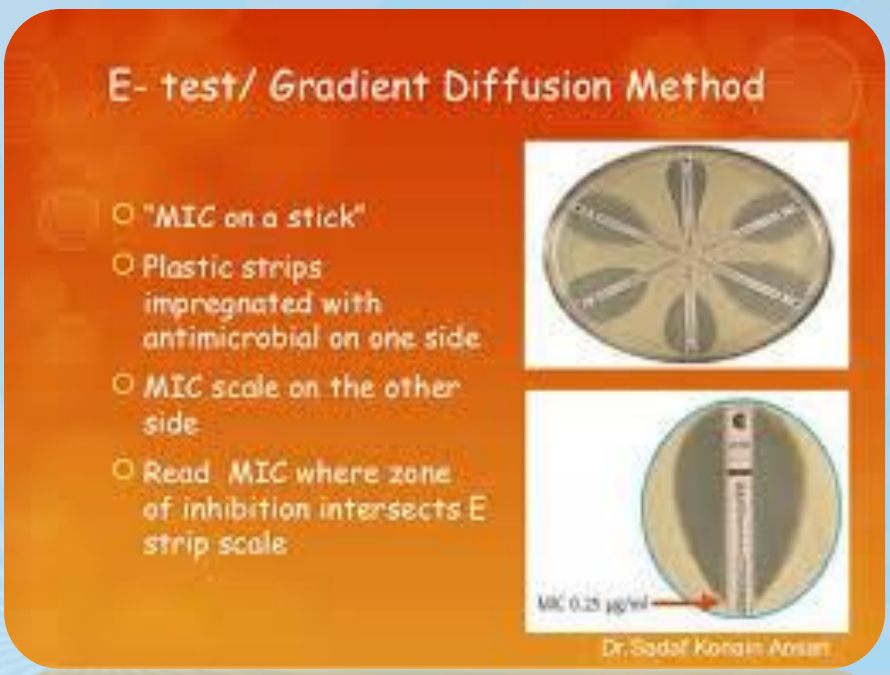
Antibiotic efficacy is tied to both concentration and time.



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In vitro Testing Methods

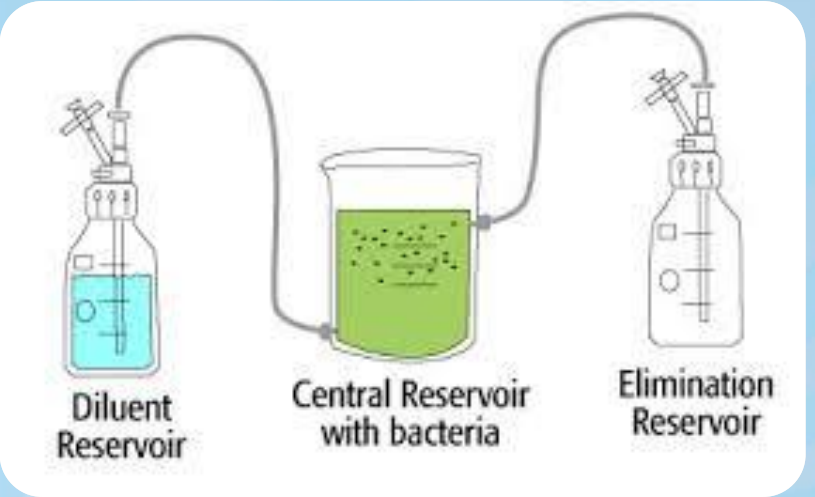
- Broth dilution test
- Antimicrobial gradient test
- Disc diffusion test
- E-test



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Assays in which both time and concentration are variable:

- Static kill assay
- Mouse thigh infection model
- Hollow fiber infection model



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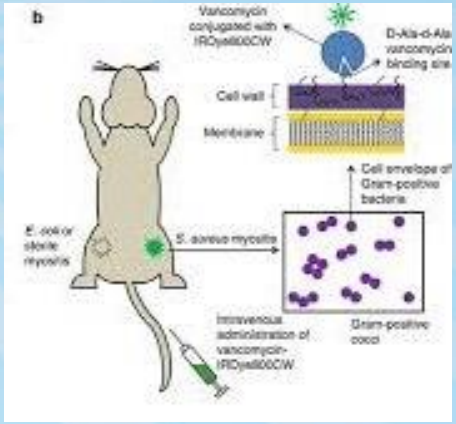
Static kill assay

- Open system, not bio safe
- Bacteria numbers change over time
- Large volume requires large amount of drug and diluent
- Rapid changes in drug concentration not possible, cannot model short half-lifes

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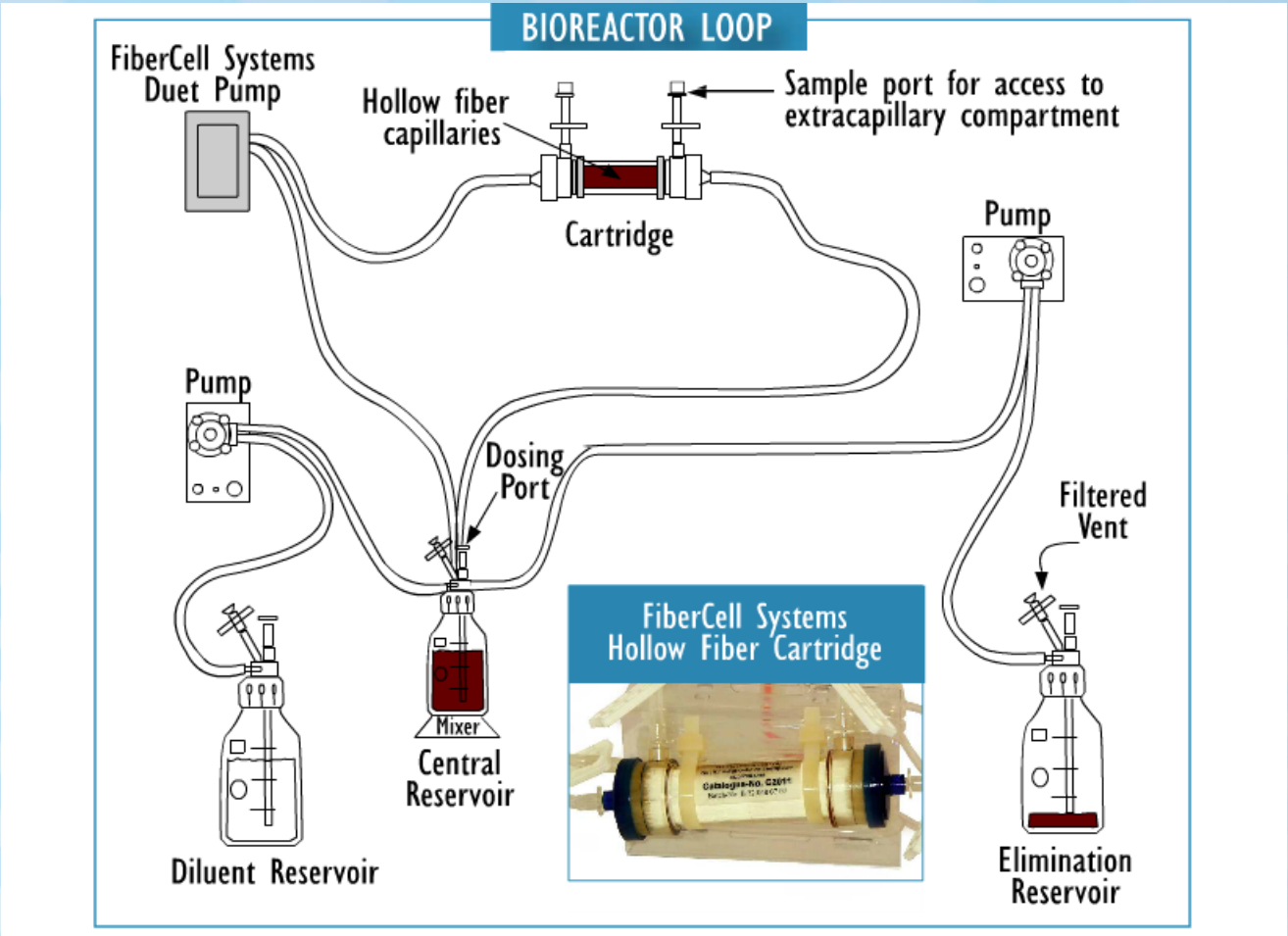
Mouse Thigh Infection Model

- PK/PD may not mimic human values
- Cannot sample over time
- Hard to do large numbers of bacteria to reveal resistance
- Many infections cannot be modeled in mouse



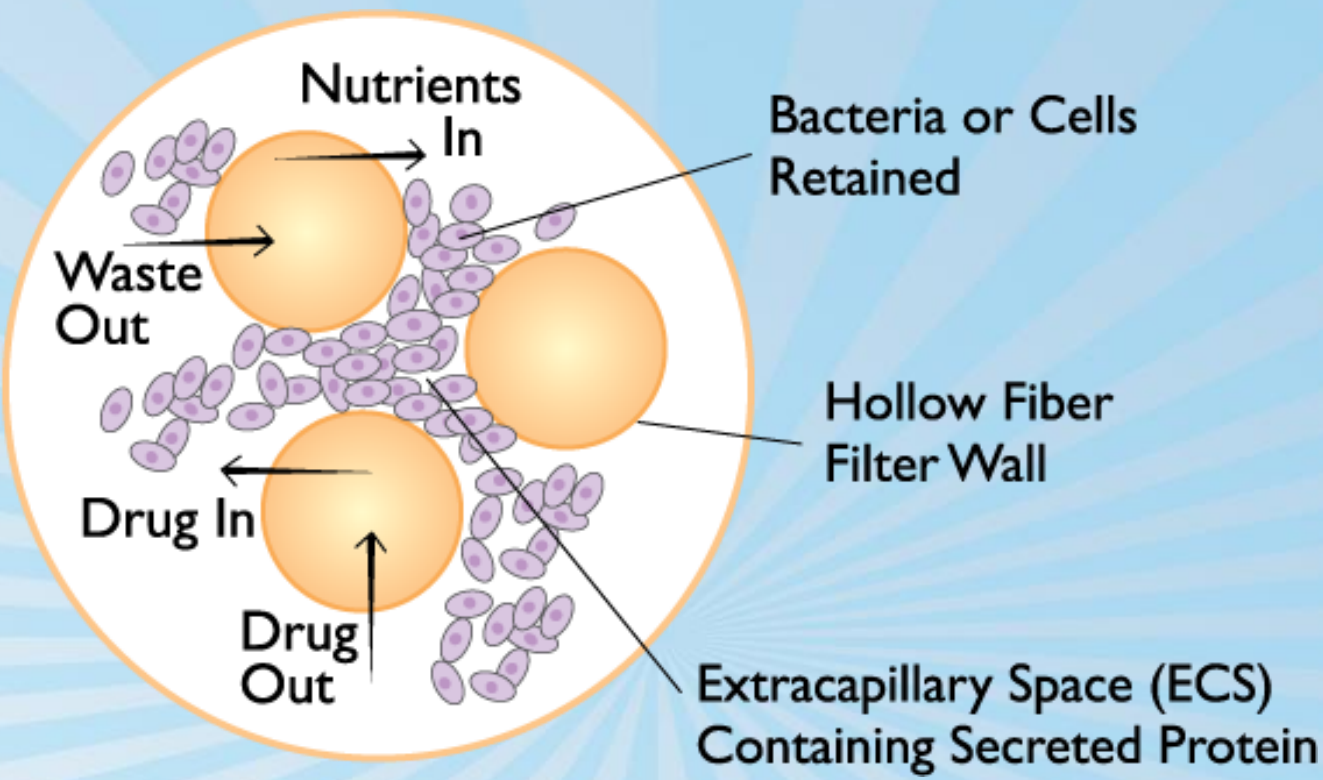
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Hollow Fiber Infection Model



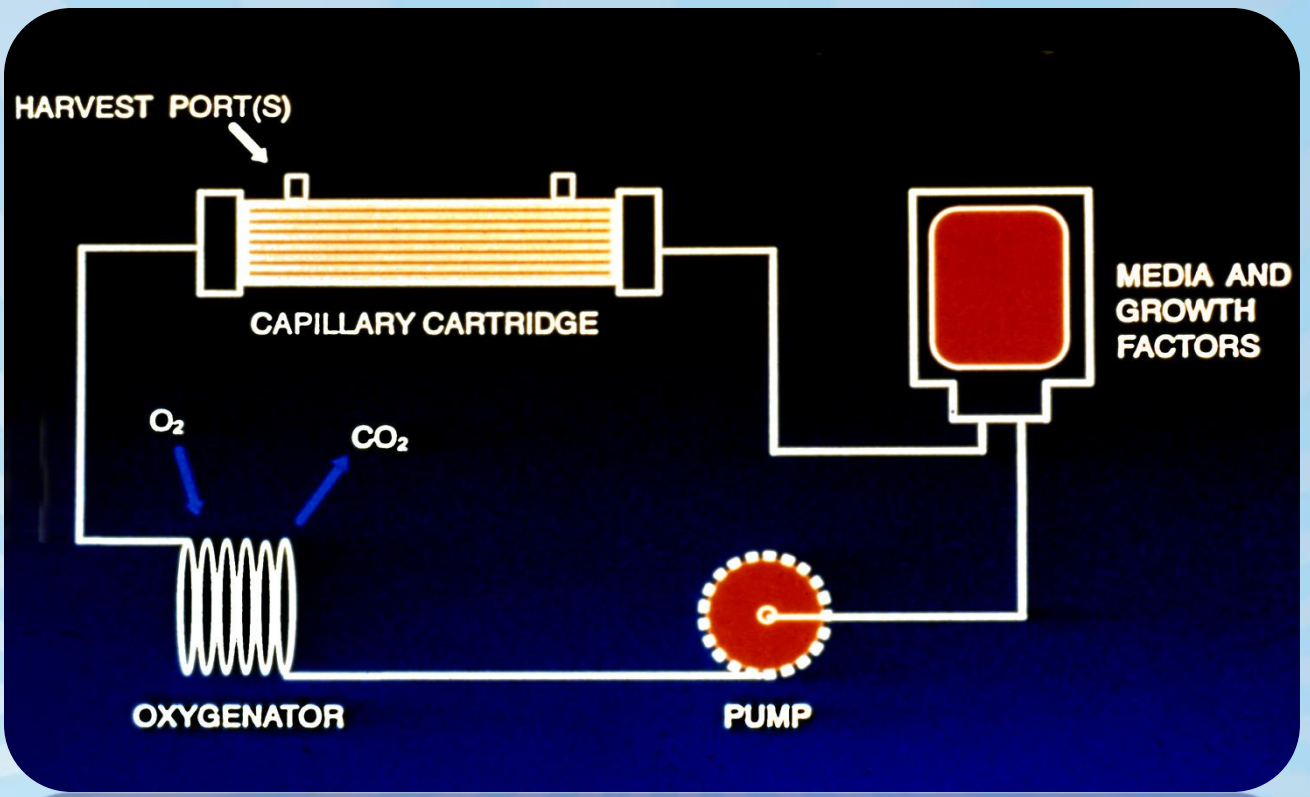
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Hollow Fiber Cross-Section



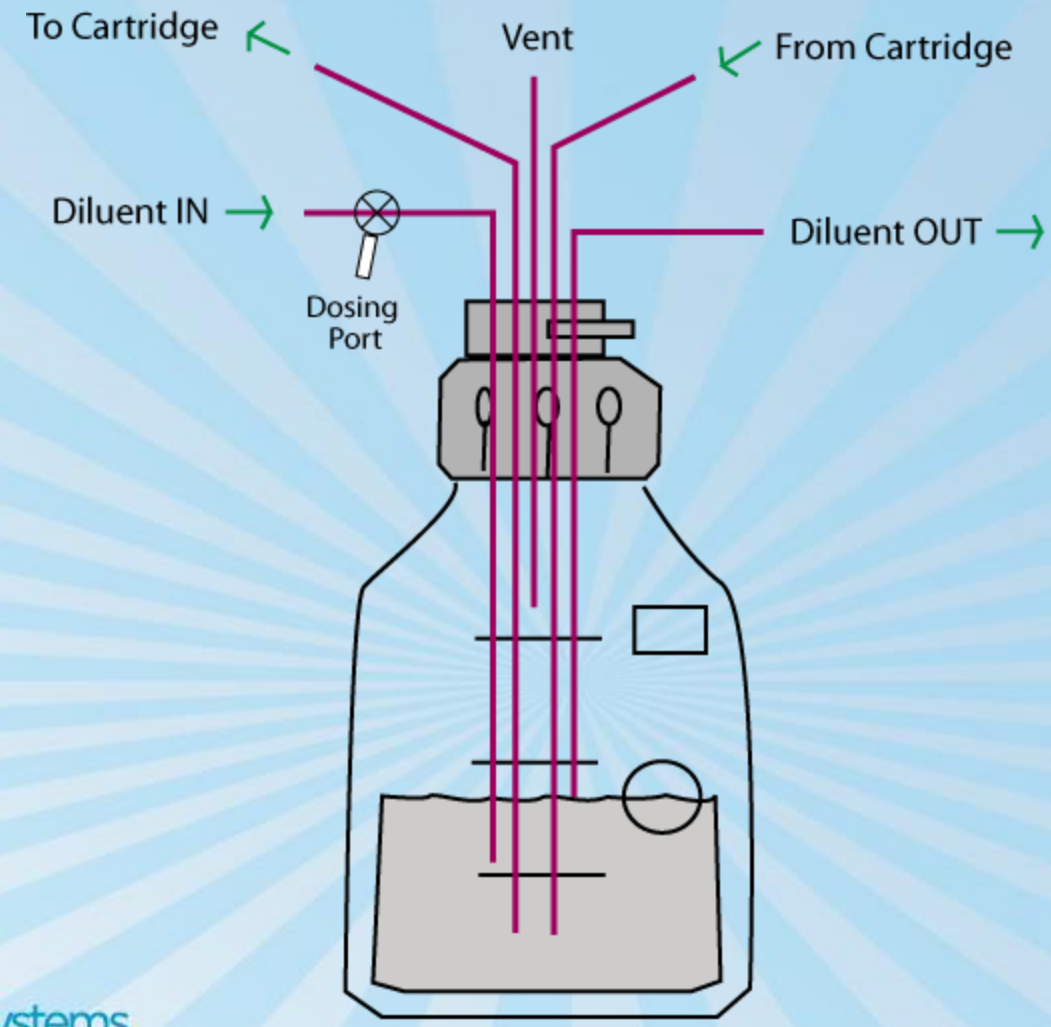
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Hollow Fiber Cartridge



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Reservoir cap



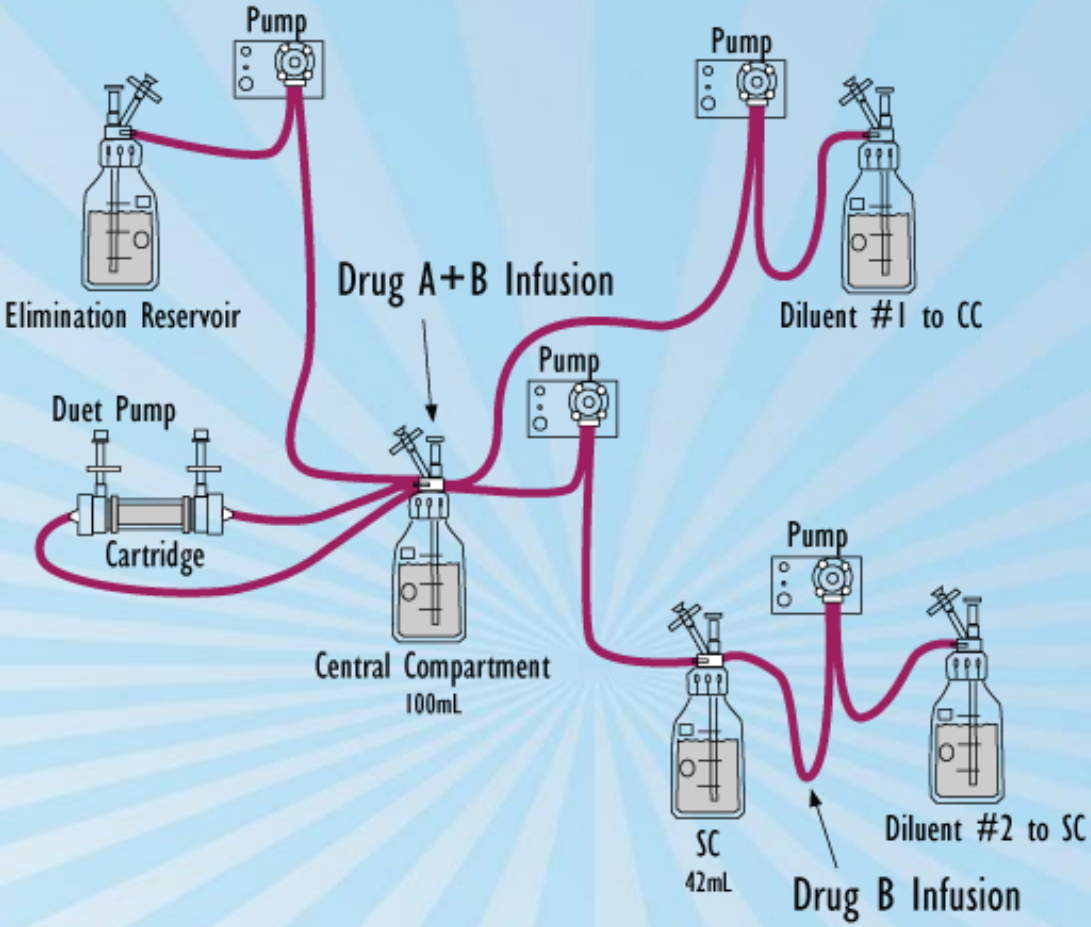
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Advantages of the Hollow Fiber Infection Model

- 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.

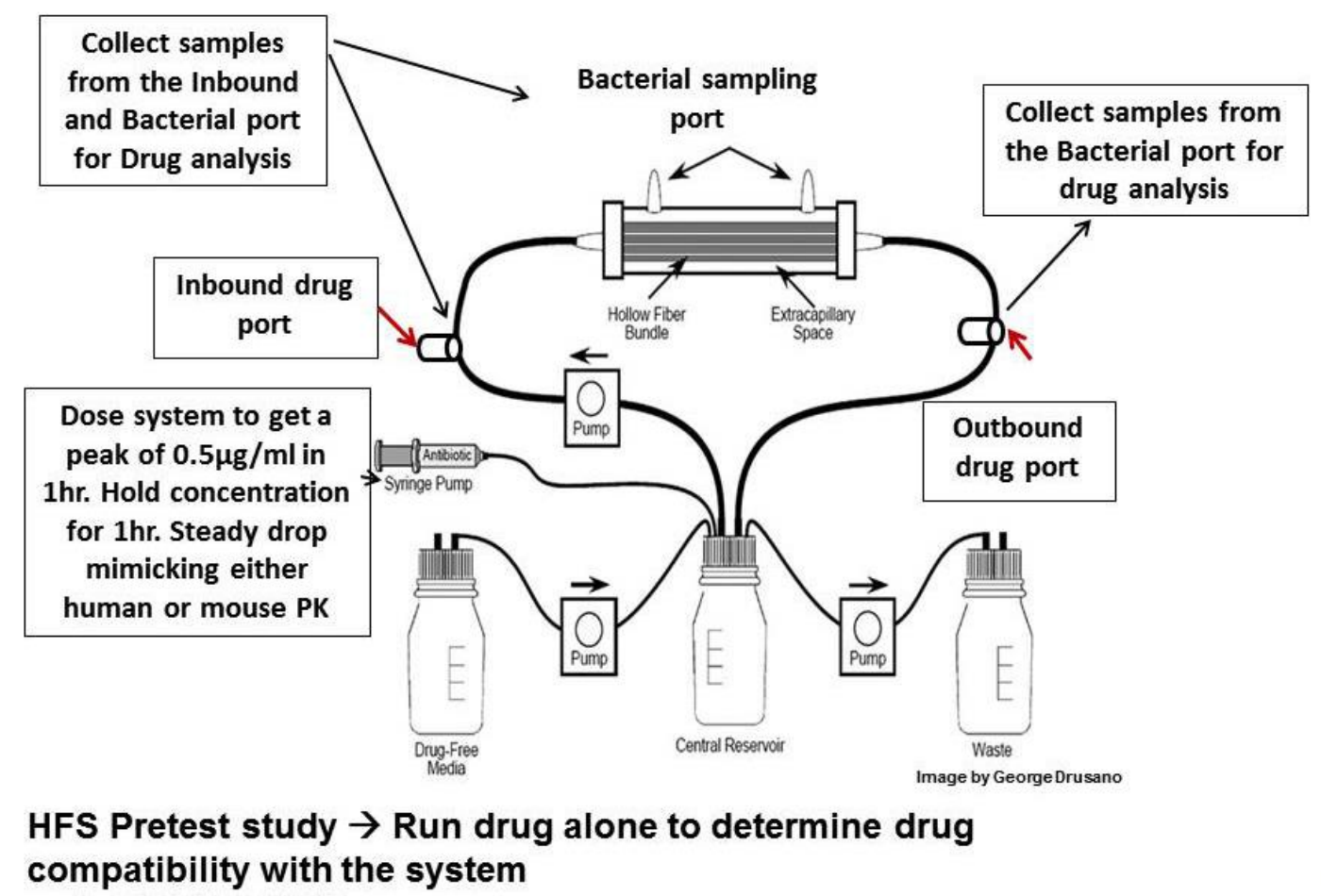
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Two Drug Model



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Hollow Fiber Pretest Study Scheme

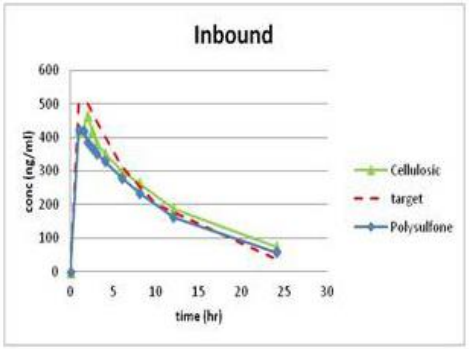


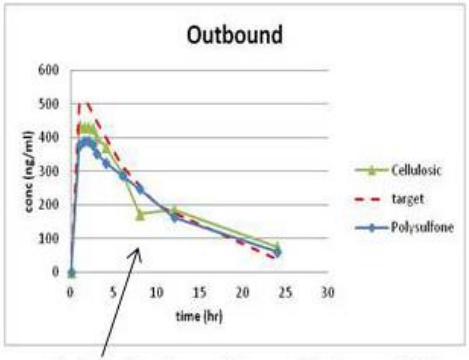
HFS Pretest study → Run drug alone to determine drug compatibility with the system

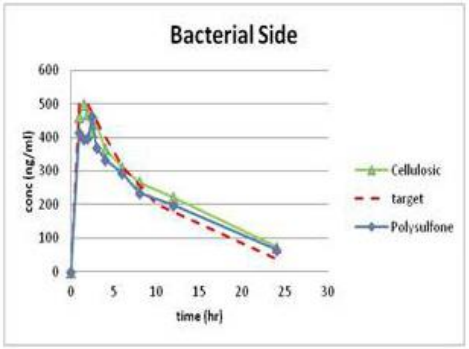
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PK Profile

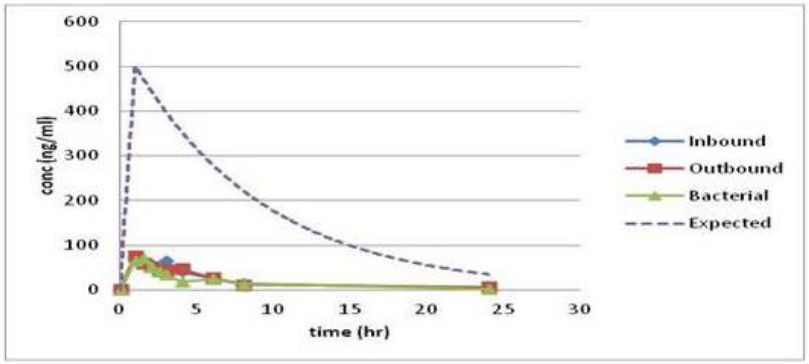
This drug showed good compatibility with both cartridges.





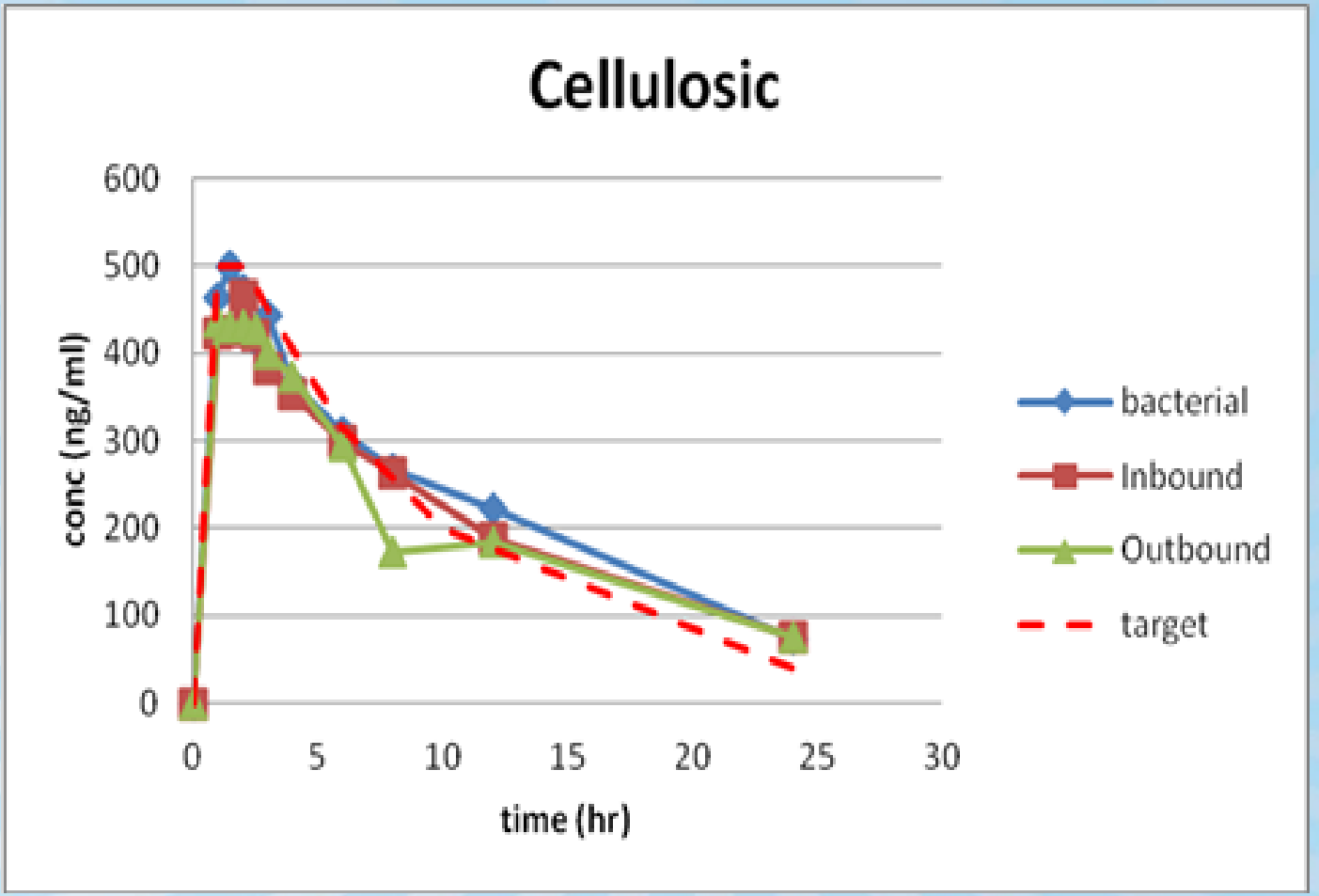


Not significant enough to consider incompatibility

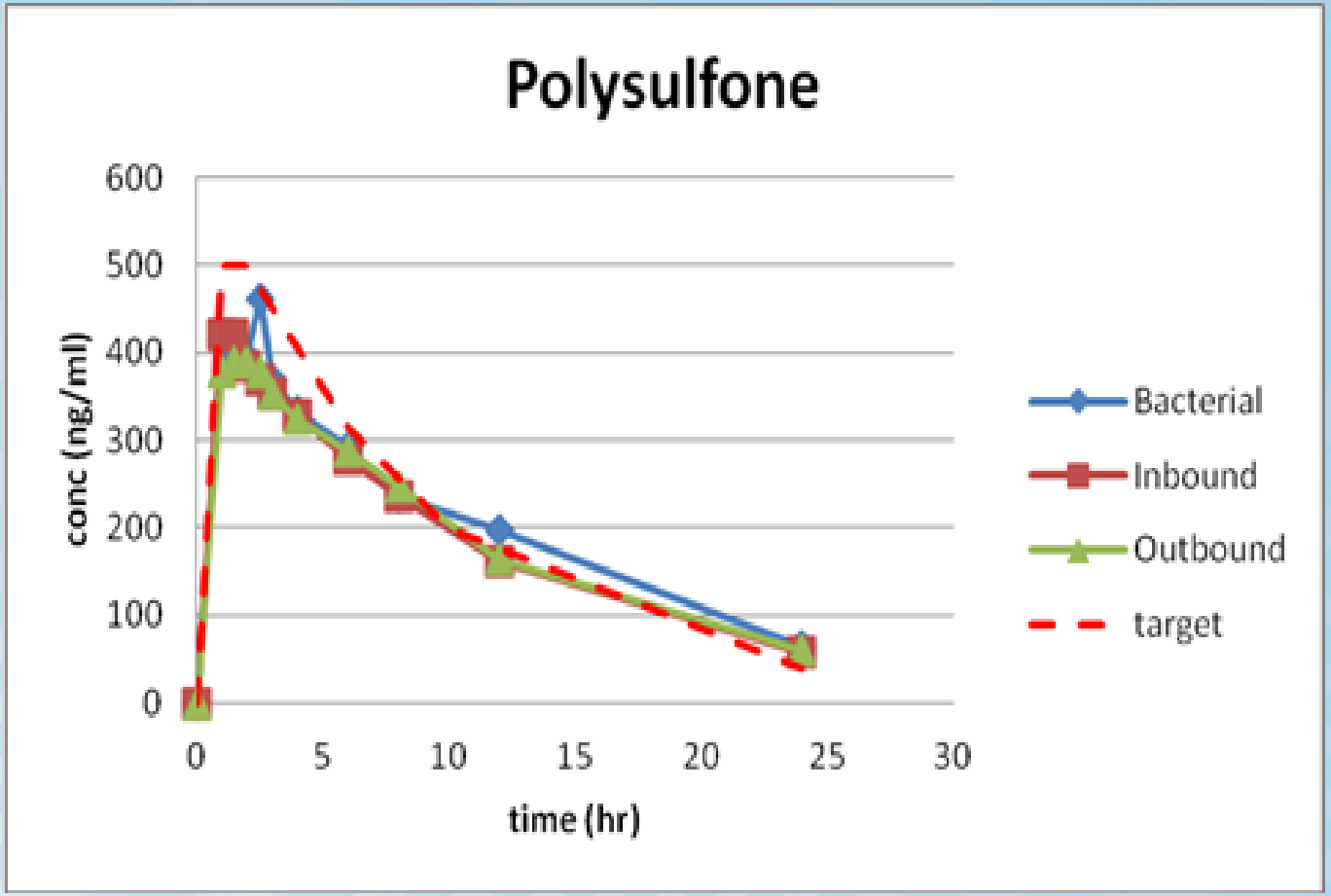


This drug is not a good candidate for HFS use

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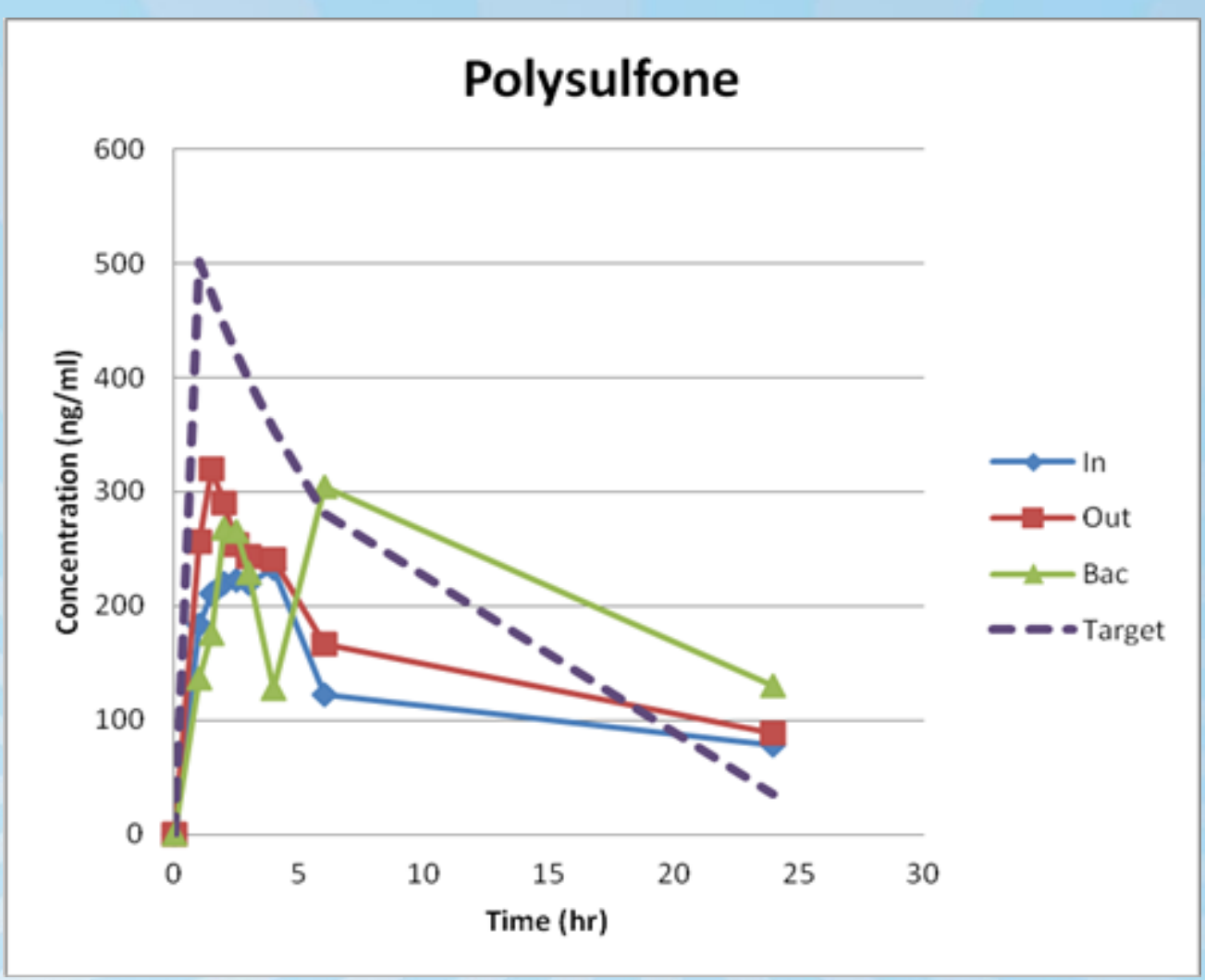


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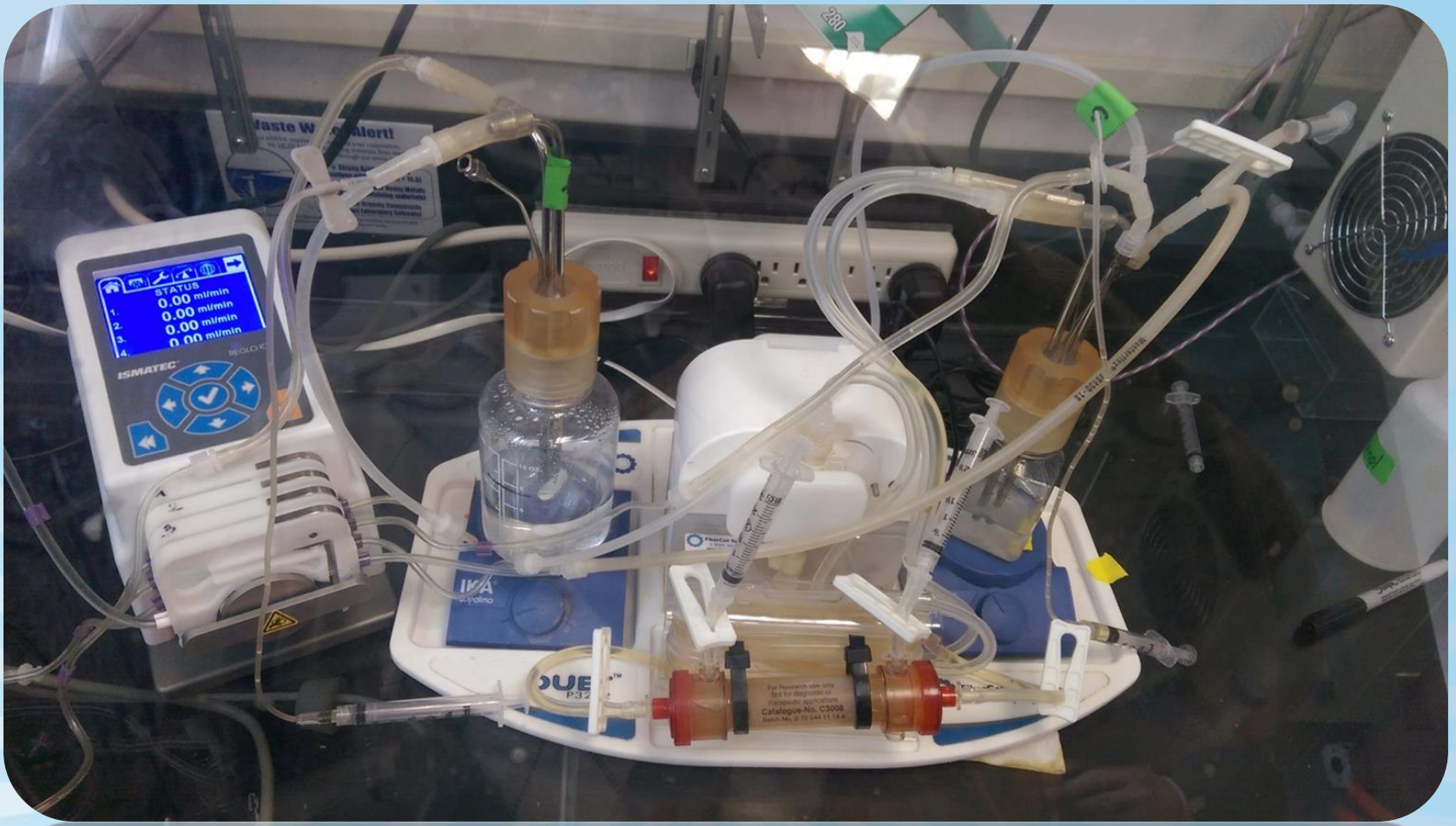




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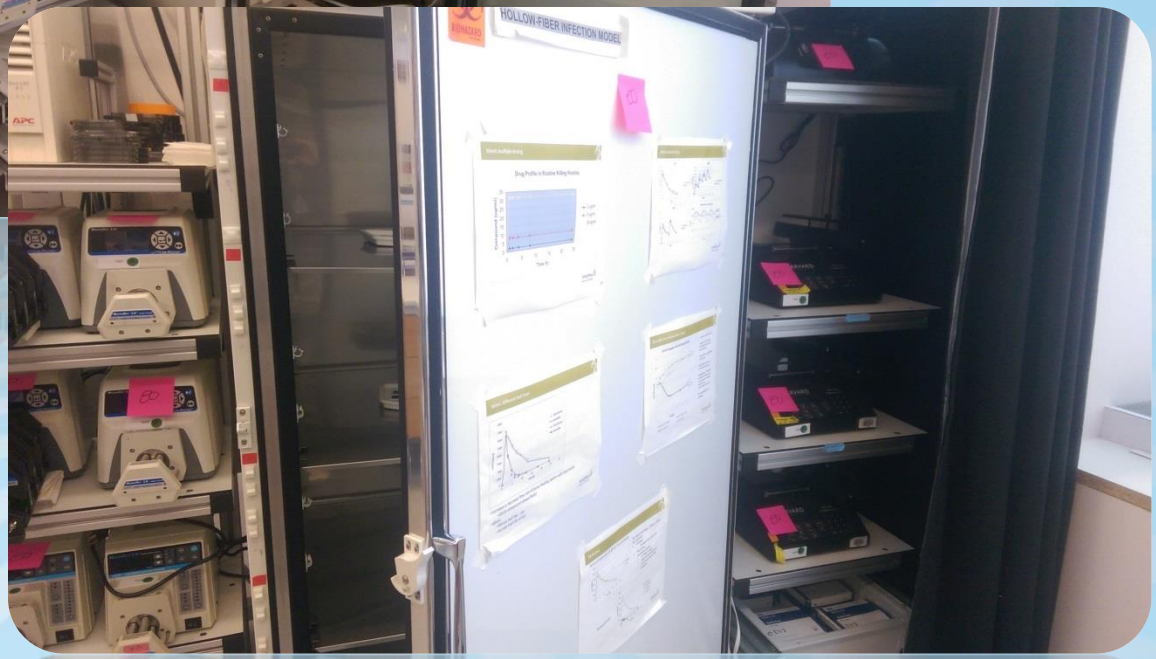


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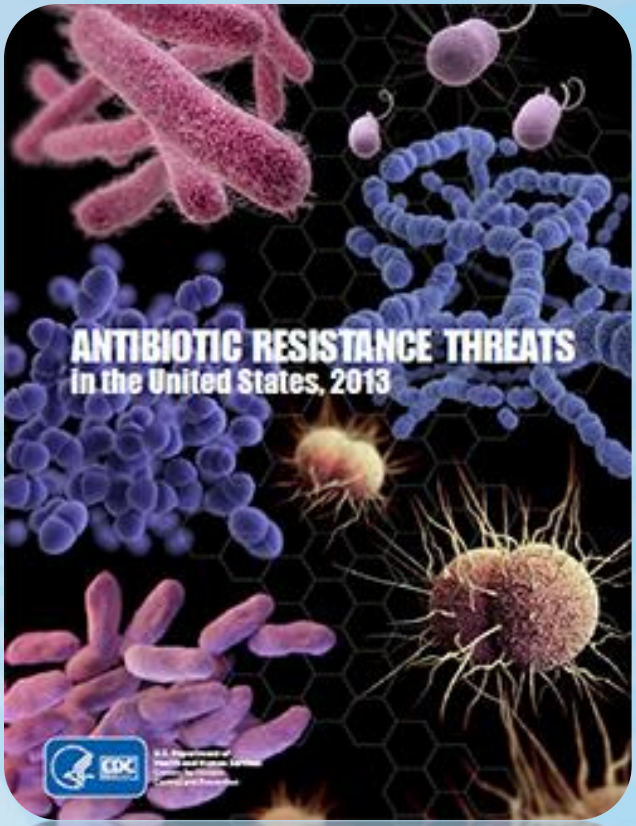




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Regulatory position

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



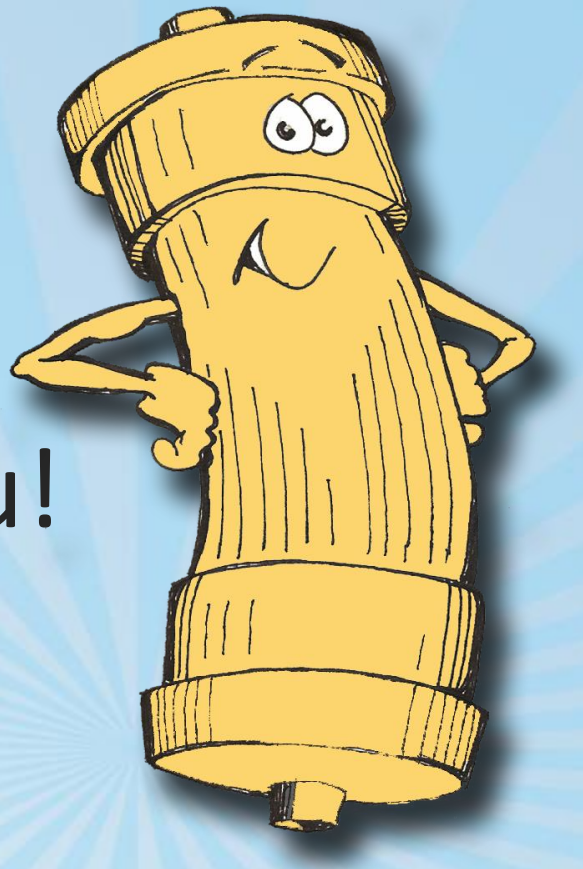
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The hollow fiber infection model is a complementary and additional tool for drug development, to be implemented at the earliest stages

- 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

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Thank you!



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