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The hollow fiber infection model: Principles and practice


Emerging antibiotic resistance presents a serious global health threat. 2 million people in the United States were infected with antibiotic resistant bacteria in 2014 and more than 20,000 died as a direct result of these infections, many more from complications. Antimicrobial resistance has been identified as one of the three greatest threats to human health. Antibiotic discovery and development require static susceptibility testing to screen compounds, *in-vitro* pharmacodynamics/pharmacokinetic (PK/PD) studies to model drug dynamics and efficacy, and testing in animal models to provide critical information prior to the clinical evaluation of new antibiotics. The one compartment PK/PD model typically consists of an open central reservoir containing the organism of interest, a source of diluent and a waste reservoir; and the disadvantages of it include open system (not bio safe), bacteria numbers change over time, large volume requires large amount of drug and diluent, rapid changes in drug concentration is not possible and cannot model the short half-lives. Animal models have many shortcomings though they have served as a primary development tool for many years because PK/PD may not match human values, cannot sample same animal over time, difficult to study large numbers of bacteria to reveal resistance and many infections cannot be modeled in a mouse or other

animal. To address these shortcomings the two-compartment *in-vitro* pharmacokinetic model utilizing hollow fiber bioreactors was developed, the hollow fiber infection model (HFIM). The advantages of the HFIM are as follows: Closed bio-safe system, large number of organism can be tested, revealing resistance, precisely simulates human PK/PD, repetitive sampling over time, both drug and organism, total kill can be determined, single use, disposable, reproducible, two drug models can be tested, can model both dosing curve and elimination curve and can look at bacteria in different growth phases and in combination with cells. The clinical utility of the HFIM has been demonstrated and is now endorsed by the EMA. An overview of historic PK/PD models is presented and the utility of the system as it relates to antibiotics and other drugs are discussed.

Speaker Biography

John James Stewart Cadwell has received his degree in Pharmacology from the University of Miami in 1981. He spent additional time for studying at the University of Nottingham and the National Institute of Medical Research at Mill Hill, UK. In 2000, he has founded FiberCell Systems Inc., a company specializing in the research and supply of hollow fiber bioreactors. He has over 10 publications in the field and three patents relating to hollow fiber systems and he is considered as a world expert in the field.

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