

# Redefining Infectious Disease Therapy

## The PULSYS™ Technology Platform

### Novel Discovery

It began with a question. In 1999, the problematic trends in the anti-infectives market—multiple daily dosages, lengthy treatments, and overuse of antibiotics—prompted the founders of MiddleBrook™ to search for a better way to attack bacteria. Would front-loading and pulsing antibiotic dosing make a difference? The answer came with a novel biological finding.

MiddleBrook scientists have made an exciting discovery. Bacteria exposed to antibiotics in short repetitive bursts—or pulses—are eliminated more efficiently and tend not to develop more resistant forms. With this proprietary knowledge in hand, MiddleBrook has the potential for redefining infectious disease therapy.

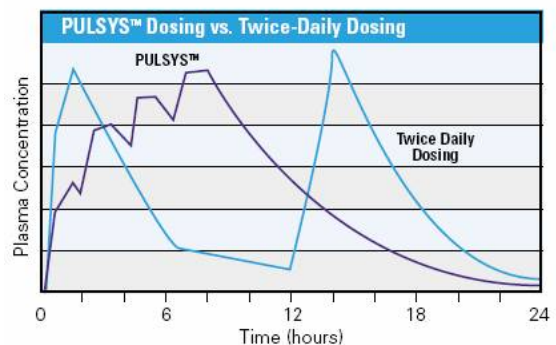
As the vehicle of this discovery, MiddleBrook developed PULSYS™, an oral drug delivery technology that enables once daily pulsatile dosing. MiddleBrook products can be designed in convenient tablet dosage forms, with possible PULSYS™ applications among a variety of drugs sold today or in the development pipeline for the \$27 billion antibiotics market.

### Preclinical Findings

MiddleBrook was founded on the premise that the efficacy of antibiotics, and anti-infectives in general, may be improved by front-loaded dosing in rapid sequential pulses. Traditional administration of antibiotics has typically been two, three, and even four times a day as immediate-release tablets or suspensions. Pulsatile dosing as conceived by MiddleBrook occurs once daily.

Pulsatile regimens have been evaluated in numerous antibiotic-pathogen systems in both *in vitro* and *in vivo* models. The results foreshadow an important shift in anti-infective dosing principles. Pulsatile dosing of certain antibiotics not only eliminated more bacteria and better prevented the development of resistant strains—it did so at significantly lower drug concentrations. A sampling of pre-clinical findings include:

- Amoxicillin can be enhanced to kill more intermediate-resistant *Strep. pneumoniae* by PULSYS™ than with the current two or three times a day dosing.
- Penicillin intermediate-resistant *Strep. pneumoniae* become resistant after two or three times a day dosing of amoxicillin, but not when dosed by PULSYS™.
- Bactericidal (killing) action for amoxicillin can be demonstrated for *Strep. pneumoniae* when dosed by PULSYS™, even at drug concentrations that are not expected to inhibit growth, let alone produce killing.
- Studies in mice suggest that the action of clarithromycin can be enhanced when dosed once daily by PULSYS™, as compared to twice-daily dosing, for both *Strep. pneumoniae* and *H. influenzae*.



# The PULSYS™ Advantage

## Technology

Based on its novel biological finding that rapid sequential pulsatile dosing of antibiotics may offer therapeutic advantages, MiddleBrook has developed the PULSYSTM oral drug delivery system and MAPS™, an enabling technology for the design of the PULSYS™ products. MAPS™ is a proprietary analysis and design system that utilizes the physical, chemical, biological and microbiological properties of each specific antibiotic to design the optimum PULSYS™ product.

The PULSYS™ dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastro-intestinal tract in a pulsatile manner. The dosage form is made up of multiple pellet types of varying release profiles that are combined in a proportion so as to produce a constant escalation in plasma drug levels in the early portion of the dosing interval. The transit properties of pellets enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms. In all cases, the MiddleBrook PULSYS™ products will be once-a-day products. The PULSYS™ system utilizes well-studied excipients and common manufacturing processes.

The development of the PULSYS™ delivery system is well advanced and clinical pharmacokinetic studies have been completed on several currently marketed antibiotics with varying therapeutic and physico-chemical profiles. MiddleBrook has a strong intellectual property position with 43 U.S. and PCT applications filed on the therapeutic benefits of pulsatile dosing and the associated drug delivery technologies. Sixteen of these patents are issued and allowed to date. In addition to antibiotics, MiddleBrook believes that this approach may find utility in antiviral and antifungal therapies to expand its anti-infectives franchise. Applications in oncology could further expand MiddleBrook's focus over the mid- to long-term. The MiddleBrook patent estate covers all of these opportunities.

## The PULSYS™ Advantage

MiddleBrook™ products under development may provide patients with more convenient alternatives to current antibiotics, making treatment regimens easier to follow. Each is designed to be taken orally, once daily. But the benefits may go much further. For some antibiotics and infections, the duration of therapy could be significantly reduced. For others, a lower daily dose may be achievable. MiddleBrook plans to market all products as once daily treatments with most dosing regimens targeted for three to five days. This is in significant contrast to currently available drugs, which are taken two, three, or four times a day for as long as 14 days. There may be one or more products consisting of a single dose for the entire treatment of a particular infection. Studies in human subjects show that the PULSYS™ system performs well in terms of strong pulses, as demonstrated by appropriate blood levels.

### **The PULSYS™ Advantage**

- Improved efficacy or killing efficiency
- Reduced bacterial resistance
- Once-daily dosing
- Shorter overall duration of therapy
- Lower daily dose
- Improved side effects profile