OVERVIEW OF LAL TEST TECHNOLOGY

Endotoxin Testing: The rabbit fever test was the standard FDA-approved test for endotoxins (pyrogens) until the approval of the LAL test by the FDA in the 1980's. The LAL test became the assay of choice for bacterial endotoxins worldwide because of its specificity, simplicity and remarkable sensitivity.

The Horseshoe Crab: Limulus Amebocyte Lysate reagent is prepared from the circulating blood cells of the horseshoe crab (Limulus polyphemus). This procedure does not harm the donors which are returned to their natural ocean environment.

Development of LAL: As early as 1885 W.H. Howell of Johns Hopkins University described the clotting of Limulus blood; however, it was not until the 1950s that Dr. Frederick Bang identified endotoxin as the causative agent for clotting. The gel-clot LAL technology was pioneered in the 1960s and early 70s by a team of Johns Hopkins scientists, Dr. Bang, Dr. Jack Levin and Dr. James F. Cooper (founder of Endosafe). Dr. Cooper's research in 1969-1971 demonstrated that the LAL test was much more sensitive than the rabbit test and that LAL reactivity (gelation and increased opacity) correlated with endotoxin concentration and biological activity. Dr. Cooper's publication in 1975 showed that endotoxin contamination caused aseptic meningitis in patients following intrathecal administration of radioactive drugs for nuclear cisternography. The products causing adverse reactions when injected into cerebral spinal fluid had passed the rabbit test, but Dr. Cooper showed that the same products gave positive results when tested for endotoxin by the new method.

Charles River Products: Endosafe® LAL is distributed throughout the world. In addition to traditional gel-clot LAL, Endosafe provides a full range of

quantitative LAL products utilizing novel colorimetric and turbidimetric assay systems.

CHARLES RIVER'S LAL TIMELINE	
1987	Endosafe®, Inc.Founded by Dr. James F. Cooper in Charleston, SC
1989	FDA product and establishment licenses received.
1991	FDA approval for Kinetic-turbidimetric assay (KTA) product received
1994	Endosafe® becomes a division of Charles River Laboratories, Inc.
1994	FDA approval for Chromogenic methodology received
1995	Charles River Endosafe® receives ISO-9002 Certification
1996	Automated LAL System introduced
1997	Turbidimetric reagent, KTA^2, introduced
1998	Biotrend™ LAL database trending software released
2000	Charles River releases EndoScan-V™ software Harmonized BET is published
2001	21 CFR Part 11 compliant software Total Endogration™ robotics system
2003	Endosafe®-PTS™ introduced for R&D applications
2003	Endosafe®-IPT for *in vitro* pyrogen detection introduced
2004	Endosafe®-PTS™ Gram ID introduced
2005	Endosafe®-PTS™ BCA™ introduced
2006	Endosafe® Microtrend introduced
2006	Endosafe®-PTS™ for endotoxin testing licensed by the FDA