Measurement & Assessment of a Non-Contact Ultrasound Therapeutic System

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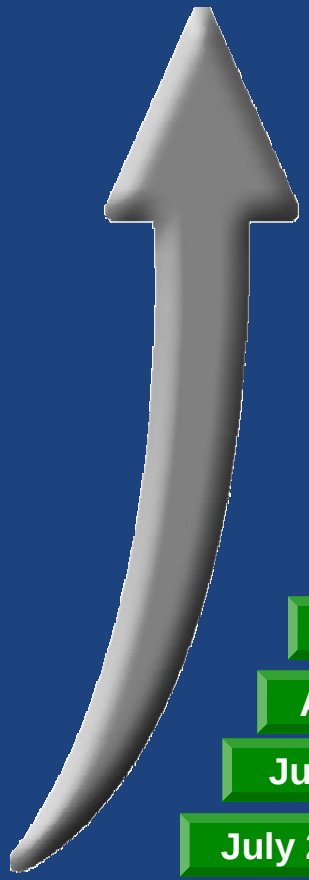
Presentation Objectives

- **Communicate key technical steps taken to address FDA Requirements to obtain market clearance to sell the MIST Therapy® System**
  - **How does the system work?**
  - **What guidelines does it operate under?**
  - **Is it consistent?**
  - **What tests have been done to prove its performance?**
  - **What has been done to provide evidence of its clinical benefit?**

Agenda

- Company Overview & Timeline
- The Celleration MIST Therapy® System
- The Commercialization Process: Integrating key product requirements into an FDA regulated ultrasound product; Focus on Ultrasound implications

Company History



August 2005	**DFU Trial Study Results Published in O/WM**
July 2005	$20 million in Series C Financing led by Triathlon Ventures
June 2005	**Second FDA Indication To Promote Wound Healing Cleared**
Dec 2004	$2.5M Convertible Bridge financing led by Prism Fund
August 2004	Initial Commercialization Team established
June 2004	**FDA 510K Initial Clearance *de novo process***
June 2004	$2.0M Series B-2 Financing Led By Affinity Capital (post-$14M)
April 2004	Patent Issued for Ultrasound Catheter Drug Delivery Device
Jan 2004	**Diabetic Foot Ulcer Study Completed**
Dec 2003	Patent Issued for Ultrasonic Wound Treatment Device
Aug 2003	Patent Issued for Ultrasound Drug Delivery Device
July 2002	**$6.8M Series B-1 Financing Lead By Affinity Capital**
July 2000	$2.0M Series A Financing From Tyco Ventures
April 2000	**Company Incorporated**

Intellectual Property

- **Celleration has 11 Patents & 5 Trademarks**
  - **Wound Healing**
    - **Energy Delivery Methods**
    - **Nozzle Configurations**
    - **Saline Delivery Methods**
  - **Catheter Drug Delivery**
  - **Oral Drug Delivery**

Non-contact Ultrasound - MIST Therapy® System

Product Indications Claim - FDA Cleared via De Novo and 510K

- **Initial FDA Indication (De Novo):**
  - The MIST Therapy® System produces a low frequency ultrasound-generated mist for wound cleansing and maintenance debridement through removal of yellow slough, fibrin, tissue exudates or bacteria
- **Second Indication was approved in June 2005:**
  - The MIST Therapy System produces a low frequency ultrasound-generated mist used to promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.
- Indications are not wound specific

Benefits of Non-Contact MIST Therapy®

- Non-contact ultrasound does not generate heat but creates bio-acoustical effects which are therapeutic
- Pain-free vs. contact therapies
- Gentle mist application provides both wound debridement & cellular stimulation
- Lowers risk of cross-contamination
- Does not rely on increasing the temperature of the wound or surrounding area

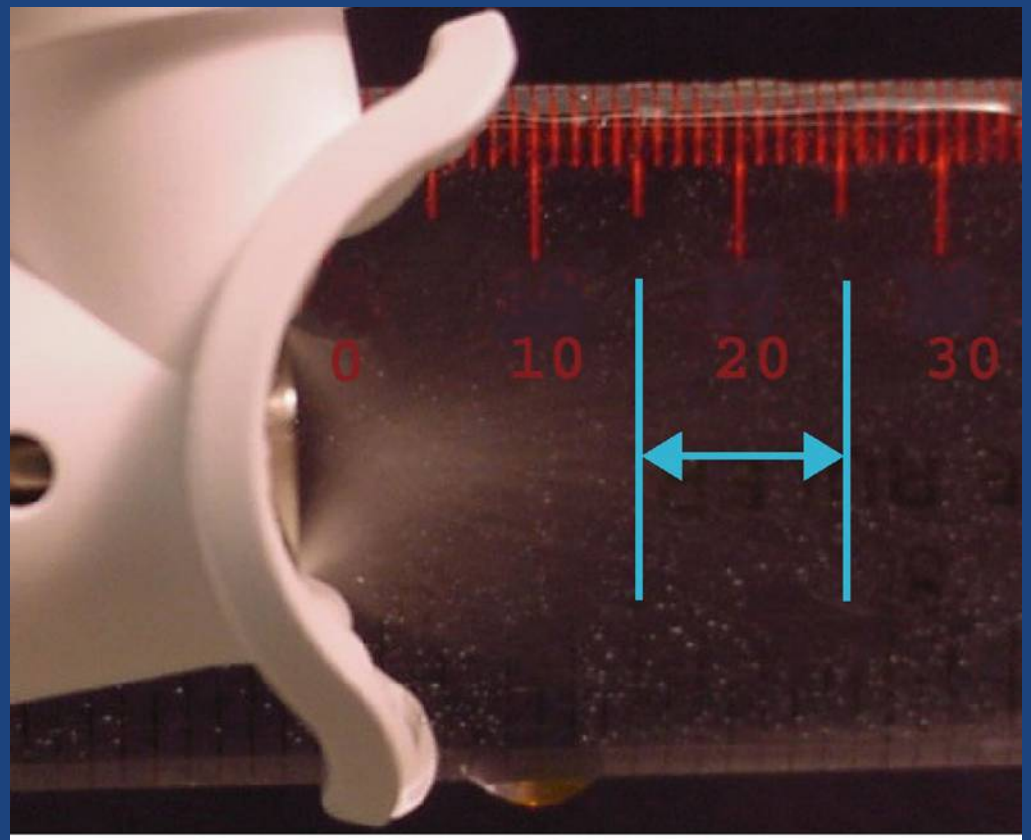
How does the MIST Therapy® System work?

- Uses a Langevin transducer design (sandwich) using a Titanium horn and aged piezoelectric wafers to generate distal tip displacement (translates in to an acoustic pressure wave)
- An applicator assembly consisting of a saline reservoir and a dispensing nozzle delivers saline to the vibrating transducer tip
- The MIST Therapy System uses continuous ultrasonic pressure wave to atomize sterile saline and deliver a continuous mist, which complements the transfer of ultrasonic energy to the treatment site
- The Treatment Process:
  - Measure wound
  - Correlate wound size to a treatment time
  - Apply mist (defined distance & pattern)

MIST Therapy® - Operating Parameters

Frequency	40 kHz
Intensity (Maximum)	1.25 W/cm^2
Intensity (Therapeutic Range)	0.1 – 0.5 W/cm^2
Distal Tip Displacement	55 - 75 microns
Tip Distance from Wound	0.5 - 1.5 cm
Treatment Time	3 - 20 min
Treatment Regimen	3x/week

Non-Contact Treatment Range



THE COMMERCIALIZATION PROCESS: Framework for Addressing FDA Requirements

- **Quality & Design Control: Are systems in place to ensure product integrity and reliability?**
  - **Quality Management System**
  - **Phased Product Development Process**
  - **Control of Records**
- **Safety: Is it safe for both the user & the patient?**
- **Efficacy: Is the product working as intended?**

Operating Guidelines

- **This is a Class II Medical Device**
  - **Utilized the Pre-market 510(k) notification process***
  - **Classified under: 21CFR 878.4410 Low Energy Wound Cleaner**
  - **ISO 13485 Compliant**
  - **IEC 60601 ETL Certified**
    - **21CFR1050, IEC 60601-2-5 guidelines except for non-contact aspects**
  - **W.H.O. Safety Limits**

Commercialization Pathway

- Non-Contact Measurement Program & Acoustical Theory: Definition of Technology Performance Capability
- Clinical Case Studies: Product Requirements Frozen
- Product Development: Phased Process; evidence of product safety, performance verification & product validation testing (V&V)
- Manufacturing Process: IQ, OQ, PQ
- Quality Systems: Documentation control, Design History Files (DHF), Audits
- Clinical Trial: Evidence of patient/user safety & product effectiveness
- Customer Feedback: How can we make it better?

QUALITY & DESIGN CONTROL:
Measurement Program

- Acoustic characterization performed for several reasons:
  - Regulatory Submissions
  - Process Control and Product Improvements
  - Support Clinical Research effort
- Characterization included both theoretical analysis and direct experimental measurements
- Concordance of theory and measurement verify the accuracy of each

Acoustic Theory

- **Pressure field from radiating face derived from monopole source theory (see IEC 61847):**

$$p = \frac{j\rho_0 \omega^2 A \delta e^{-jkr}}{4\pi r}$$

where ρ_0 is the density of air, ω is the angular frequency ($2\pi f$), A is the area of the radiator, and δ is the amplitude of the tip displacement

- **The finite dimension of the tip produces a slightly directive beam pattern, based on the function:**

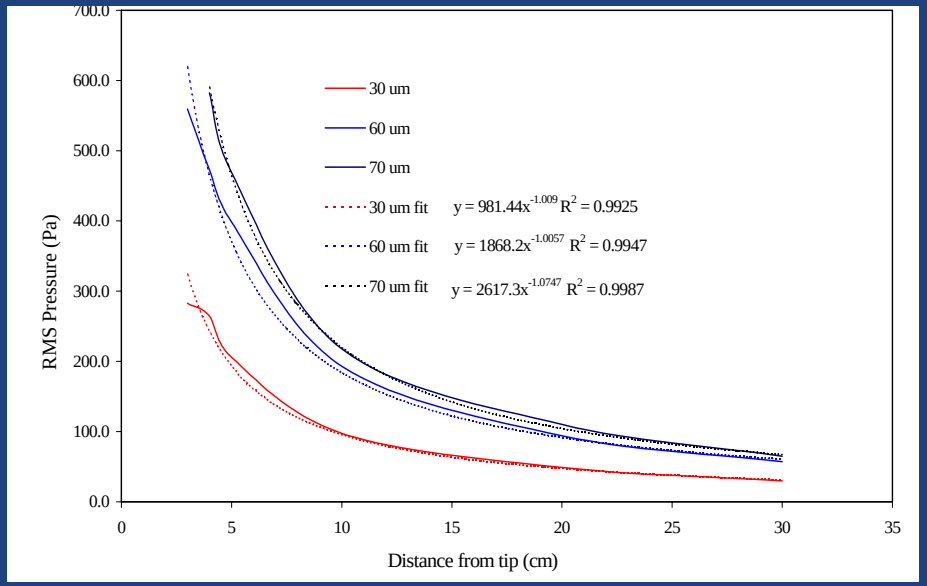
$$P \propto \frac{J_1(ka\sin(\theta))}{ka\sin(\theta)}$$

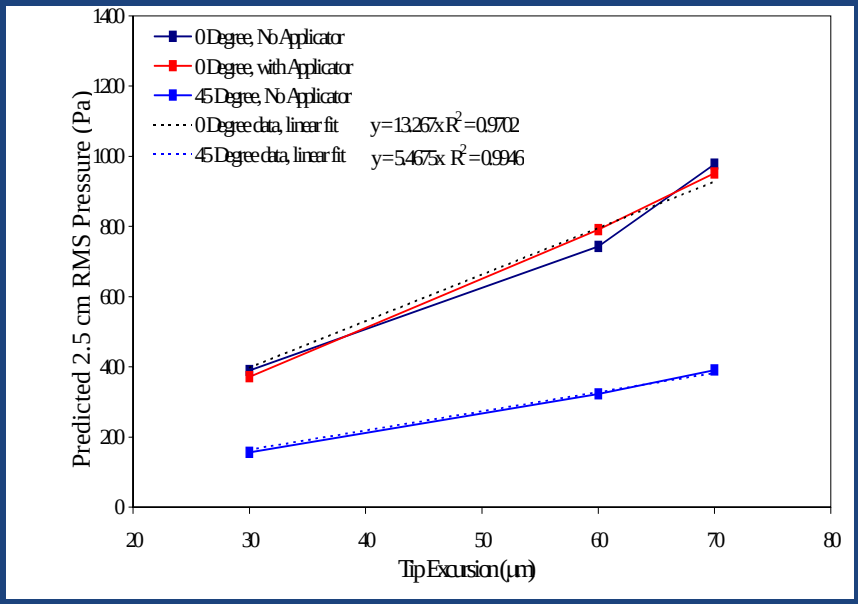
where $J_1(x)$ is the first order Bessel function, k is the wavenumber (ω/c), a is the radius of the piston, and Θ is the angle with respect to the plane of the radiator

Measurement Techniques

- Accurate results required proper use of microphone, hydrophones, sound absorption materials, water tanks, etc.
- Issues with reflections and standing waves were commonplace

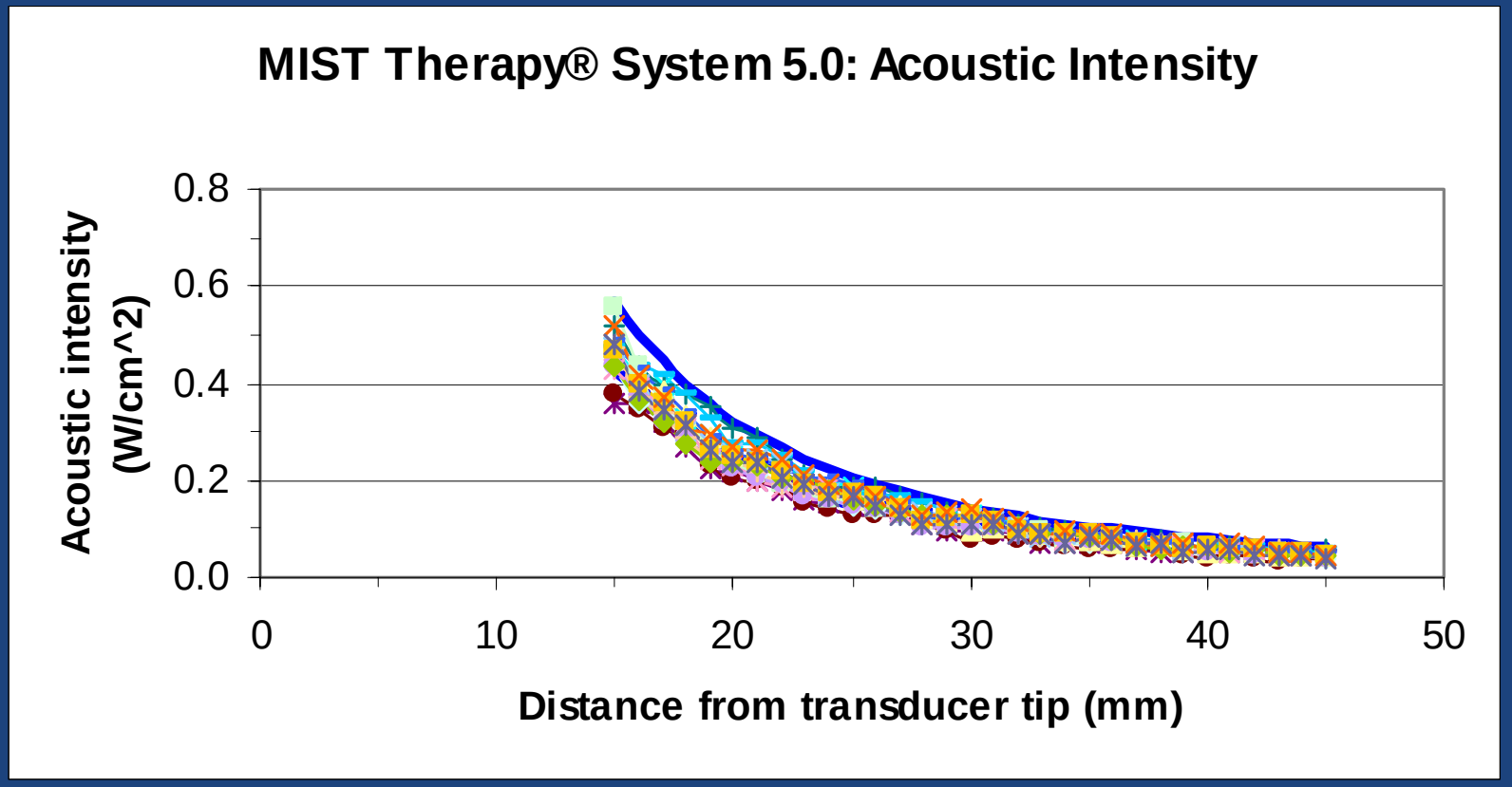
Theory vs. Experimental Test Results





- Theoretical predictions matched the experimental results to within five percent at clinically relevant distances and angles
- Since each approach was independent, this provided a verification of their accuracy

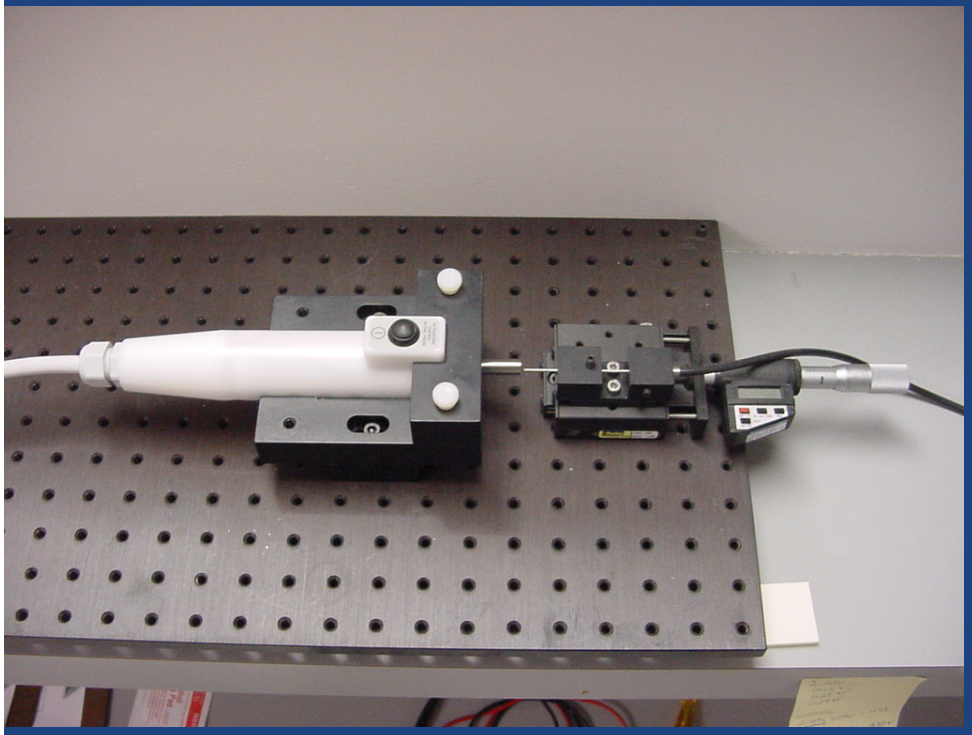
Production Testing: System Design Integrity



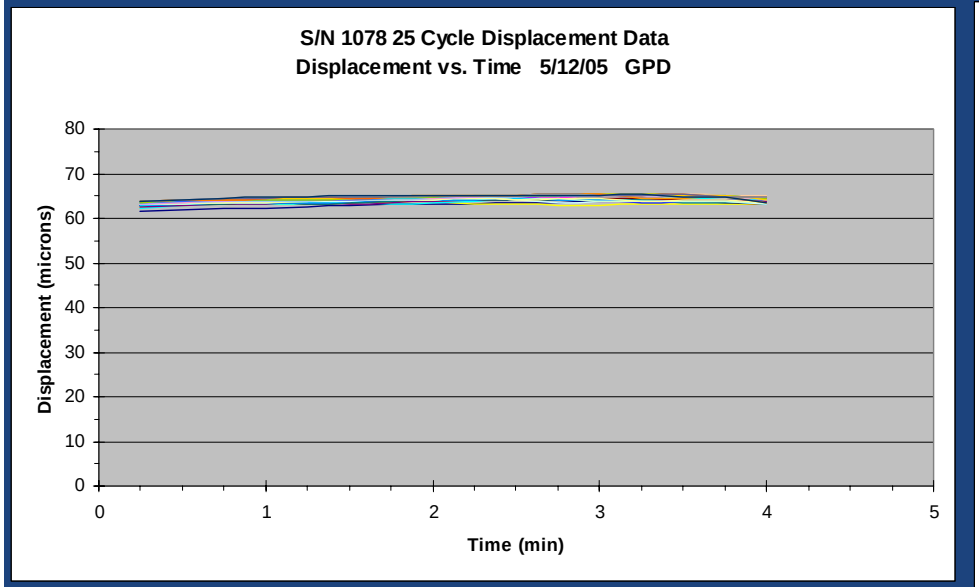
Conversion to Production Acceptance Criteria

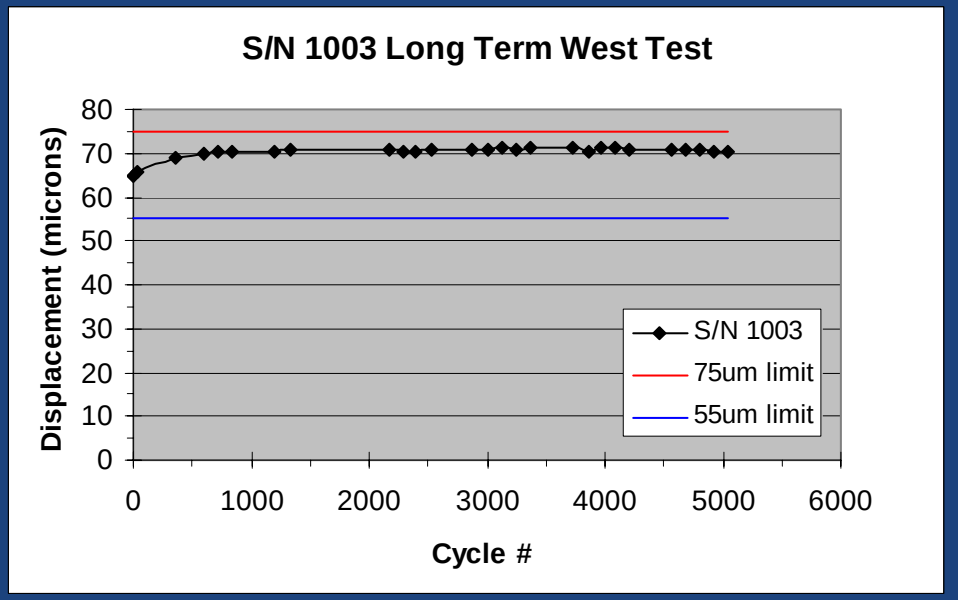
- Acoustic output is driven by frequency, surface area and mechanical displacement of the transducer tip
- Strong correlation between acoustic output and theory enables distal tip displacement measurements to serve as reliable production tool to gauge acoustic output
- The MIST Therapy® System acceptance criteria is based upon meeting a +/- 10µm displacement tolerance over a minimum of 25 simulated operational cycles

Vibrometer Displacement Testing: Production ATP and Safety Testing



Displacement Cycle Testing: ATP & Endurance Testing

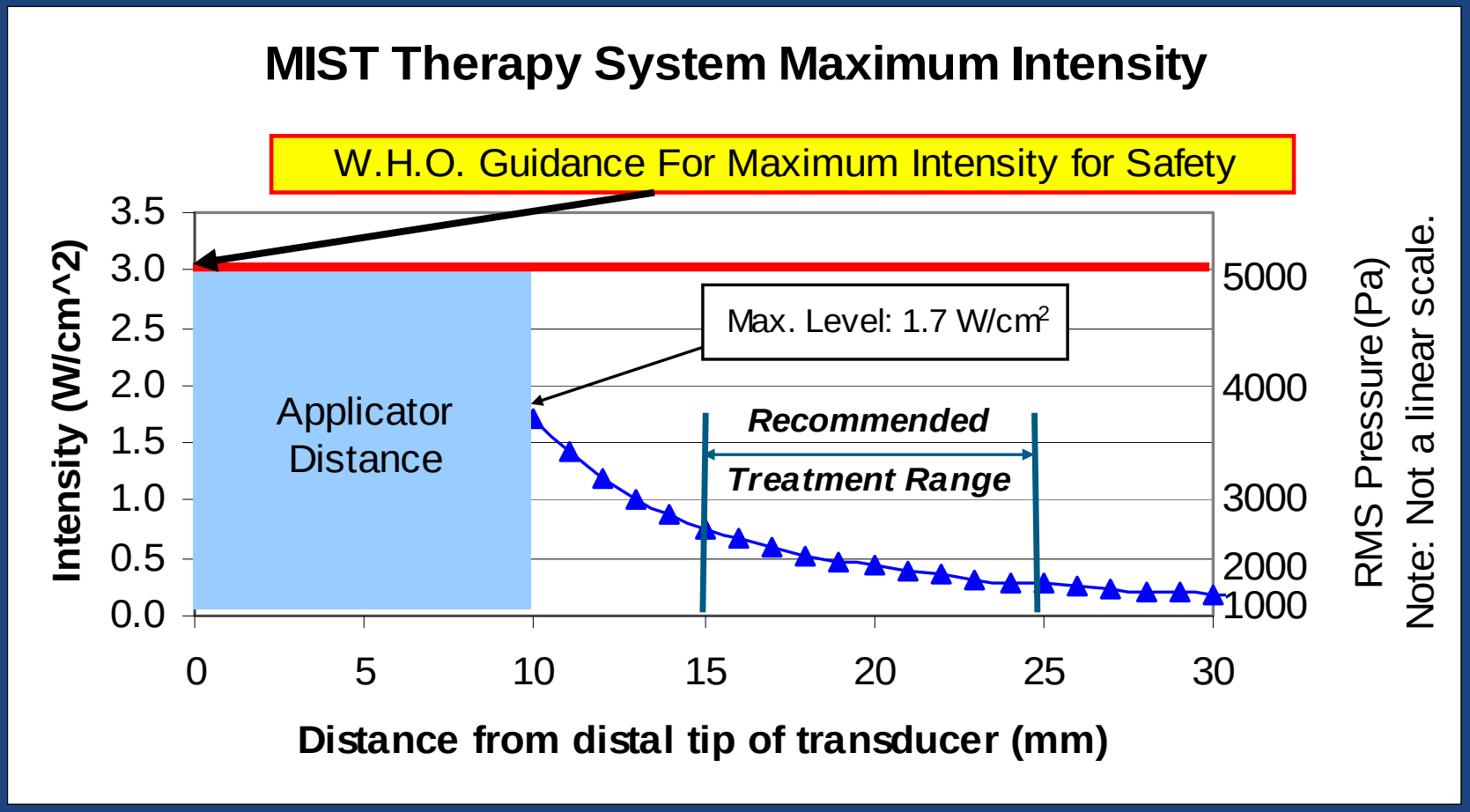




Key Safety Considerations

- Identification of maximum energy levels
  - Patient Levels: <3.0 W/cm²
  - User Levels: unwanted radiation <100mW/cm²
- W.H.O. human interface temperature limits
  - Patient Levels: Mist must not exceed 41°C
  - User Levels: Hand-piece must not exceed 41°C
- Nozzle configured to prevent inadvertent contact with transducer
- Aerosolization Testing conducted with Anderson Air Sampler to demonstrate that MIST Therapy® does not aerosolize contaminants

Is it Safe?: MIST Therapy® – Intensity Curve



Efficacy: Is the product working as intended?

Science Based Evidence for MIST Therapy

- *In Vitro : Human fibroblast studies*
- *Animal: Diabetes induced mouse study*
- *Animal: Bacteria reduction porcine study*
- *Clinical: Pressure ulcer study*
- *Clinical: Mayo Clinic study in lower limb ulcers*
- *Clinical: Advocate Christ study in wounds of various etiologies*
- *Clinical: Diabetic foot ulcer study*

Elements Critical to the Healing Process

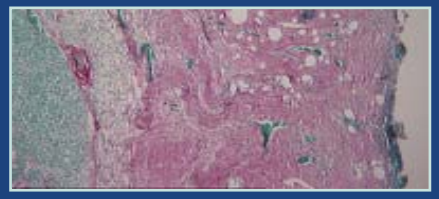
T = 0

CRITICAL HEALING PROCESS

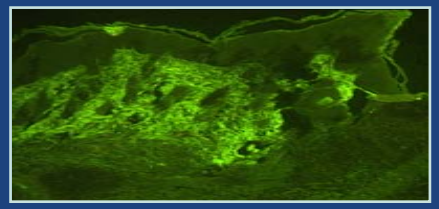
Debridement

Bioburden Management

Increases Blood Vessel Growth and Circulation



Cellular Stimulation

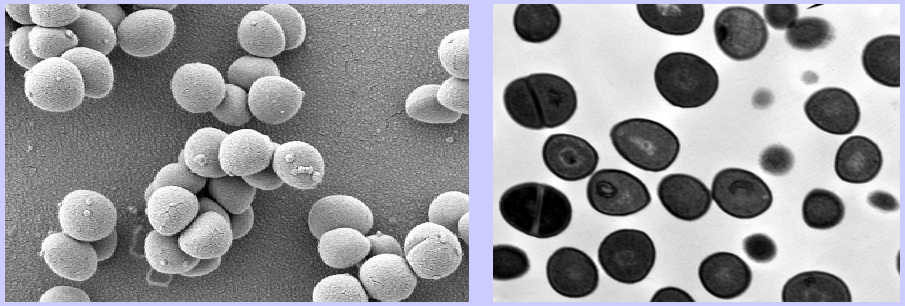


T = 12 Weeks

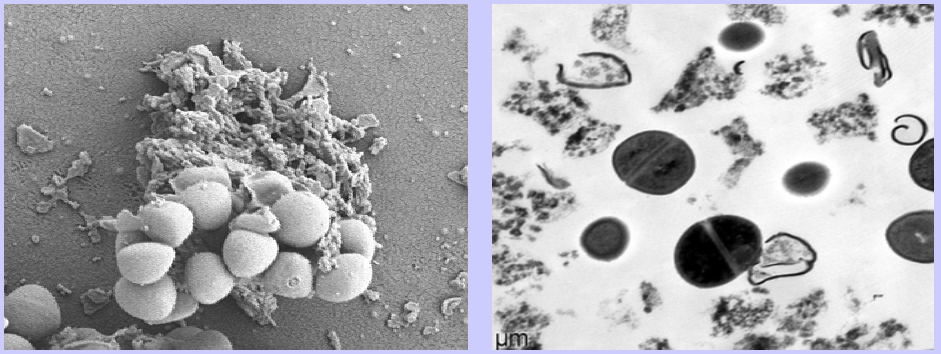
Case Study: Bacterial Effect

Gonda Wound Center at Mayo Clinic (Dr. S. Kavros and Dr. F. Cockerill)

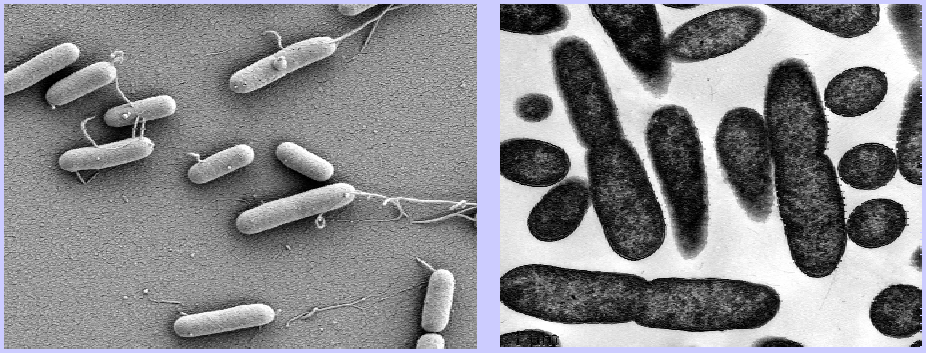
SEM / TEM 40k Mag
Staph. aureus Control



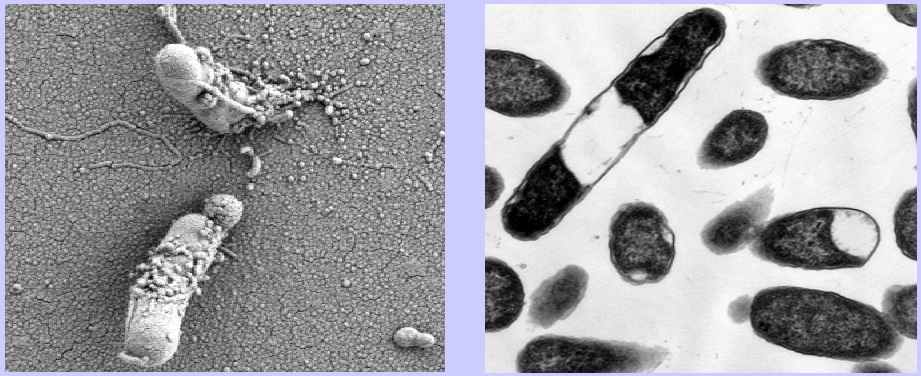
SEM / TEM 40k Mag
Staph. aureus Experimental



SEM / TEM 40k Mag
P. aeruginosa Control



SEM / TEM 40k Mag
P. aeruginosa Experimental



Bacteria Reduction Study – Porcine Model

Day of Surgery

MIST Therapy – 2 Treatments

Diabetic Foot Ulcer Clinical Trial

Study Design:

- **Prospective, randomized, double-blinded, SHAM controlled comparative trial of wound closure incidence**
- **Standard of Care - moist dressing, debridement and offloading**
- **Patients had to meet 31 inclusions/exclusion criteria**
- **Multi-center, 23 investigator sites**

Conclusions:

- **55 evaluable patients; median age of wound chronicity - 39 wks**
- **Incidence of complete closure was significantly (2.9x) higher with MIST Therapy 41% vs. 14.3%**
- **Significant by both Chi-square (p=0.022) and Kaplan Meier Wilcoxin (p=0.0144)**

DFU Clinical Study: Double-blind, sham control

FEATURE

Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of A Randomized, Double-Blind, Controlled, Multicenter Study

William J. Ennis, DO; Phil Formann, DPM; Neal Mozen, DPM; Joi Massey, PT; Teresa Conner-Kerr, PhD, PT; Patricio Meneses, PhD; and the MIST Ultrasound Diabetic Foot Study Group

An estimated 15% of patients with diabetes will develop a foot ulcer sometime in their life, making them 30 to 40 times more likely to undergo amputation due to a non-healing foot ulcer than the non-diabetic population. To determine the safety and efficacy of a new non-contact, kilohertz ultrasound therapy for the healing of recalcitrant diabetic foot ulcers — as well as to evaluate the impact on total closure and quantitative bacterial cultures and the effect on healing of various levels of sharp/surgical debridement — a randomized, double-blinded, sham-controlled, multicenter study was conducted in hospital-based and private wound care clinics. Patients (55 met criteria for efficacy analysis) received standard of care, which included products that provide a moist environment, offloading diabetic shoes and socks, debridement, wound evaluation, and measurement. The "therapy" was either active 40 KHz ultrasound delivered by a saline mist or a "sham device" which delivered a saline mist without the use of ultrasound. After 12 weeks of care, the proportion of wounds healed (defined as complete epithelialization without drainage) in the active ultrasound therapy device group was significantly higher than that in the sham control group (40.7% versus 14.3%, P = 0.0366, Fisher's exact test). The ultrasound treatment was easy to use and no difference in the number and type of adverse events between the two treatment groups was noted. Of interest, wounds were debrided at baseline followed by a quantitative culture biopsy. The results of these cultures demonstrated a significant bioburden (>10^5) in the majority of cases, despite a lack of clinical signs of infection. Compared to control, this therapeutic modality was found to increase the healing rate of recalcitrant, diabetic foot ulcers.

KEYWORDS: ultrasound, debridement, diabetic foot ulcer, randomized controlled trial, wound modalities

Ostomy/Wound Management 2005;51(8):24–39

Future items to report on

- Provide findings from a double blind Clinical Study on Pain Reduction
- Report on measurement techniques and animal studies associated with depth of penetration