Use of A Medical Device Development Tool (MDDT) for Therapeutic Ultrasound Device Characterization

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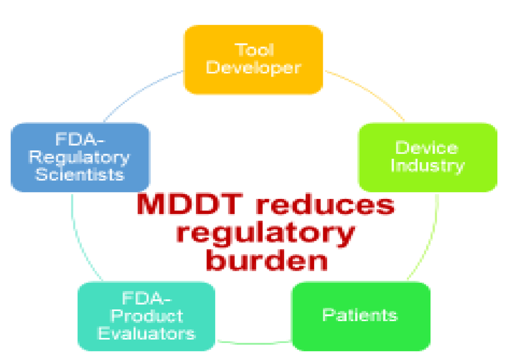
Abstract

The Center for Devices and Radiological Health at the U.S. FDA qualified the Tissue-Mimicking Material (TMM) tool for High Intensity Therapeutic Ultrasound (HITU) devices through the Medical Device Development Tools (MDDT) Program on July 10th, 2019. The qualified TMM tool (TMM MDDT) is available for HITU device developers to use in pre-clinical laboratory studies under certain conditions such that the effects of novel HITU devices can be assessed in a reliable and predictable way. The TMM is a hydrogel-based tissue mimicking material phantom and when embedded with thermocouples, it can provide spatial temperature heating and cooling profiles under HITU device exposures. To date, the TMM has been used to investigate thermally significant HITU-induced cavitation activity and corresponding temperature variations with ex vivo swine muscle tissues. Reasonable agreement between HITU numerical simulation and experimental temperature measurement has also been achieved using this phantom material. During a HITU multi-stakeholder research initiative funded by DARPA [Deep bleeder acoustic coagulation (DBAC) project], engineers from Siemens Ultrasound Division and UW Applied Physics Lab employed this TMM as an integrated phantom testbed (with blood flow, bone mimic and thermocouples) to evaluate an image-guided non-invasive HITU cuff system for automatic thermal coagulation of emergent internal bleeding injury in combat. This TMM phantom has also been utilized recently by University of Cincinnati and University of North Carolina to facilitate therapeutic ultrasound dosimetry and clinical studies, including ultrasound hyperthermia IR thermography, HITU nanoparticle enhancement, HITU ethanol ablation and ultrasound droplet imaging. For developers of HITU devices, understanding how their device performs acoustically in early device development stages using the TMM MDDT allow them to improve the device's performance and make modifications before moving on to assessing the device safety and effectiveness on patients. HITU device developers can use the TMM MDDT to design their final finished devices with increased confidence and with the expectation of a faster and more transparent regulatory review process. Two sponsors have recently reported the use of the TMM phantom in their premarket submissions to FDA/CDRH.

Introduction

FDA Medical Device Development Tool (MDDT) Program



Qualification: the Agency has reviewed and concurs that the tool produces scientifically-plausible measurements and works as intended.

-- Pre-clinical design and device performance evaluation can be conducted with qualified MDDT tool.

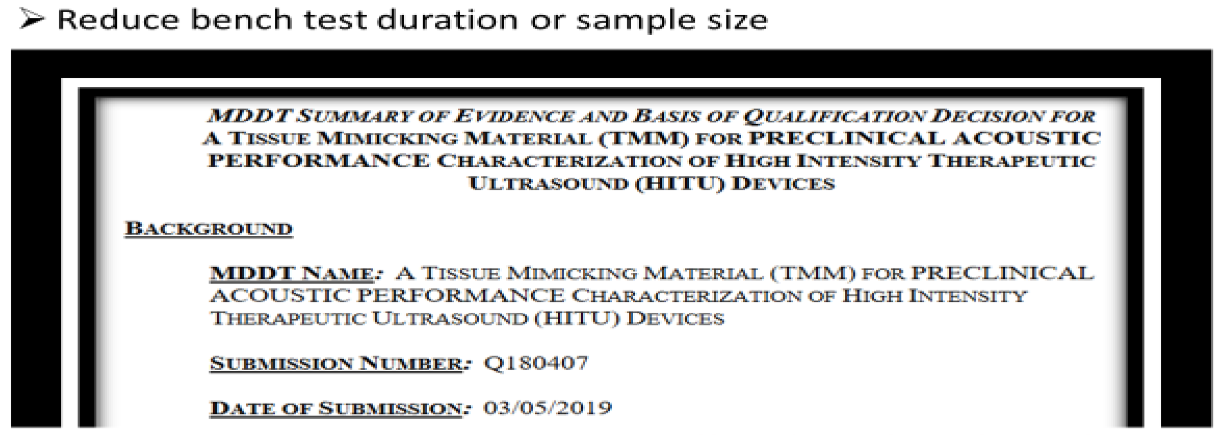
-- Post-market technical design changes can also be tested with this MDDT to streamline additional animal and clinical studies.

https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt

A HIFU Tissue Mimicking Material Qualified in July 2019

MDDT NAM (Nonclinical Assessment Model)

- A phantom to measure HIFU device preclinical acoustic performance
- Reduce / Replace animal thermal testing
- Reduce bench test duration or sample size


MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR A TISSUE MIMICKING MATERIAL (TMM) FOR PRECLINICAL ACOUSTIC PERFORMANCE CHARACTERIZATION OF HIGH INTENSITY THERAPEUTIC ULTRASOUND (HITU) DEVICES

BACKGROUND

MDDT NAME: A TISSUE MIMICKING MATERIAL (TMM) FOR PRECLINICAL ACOUSTIC PERFORMANCE CHARACTERIZATION OF HIGH INTENSITY THERAPEUTIC ULTRASOUND (HITU) DEVICES

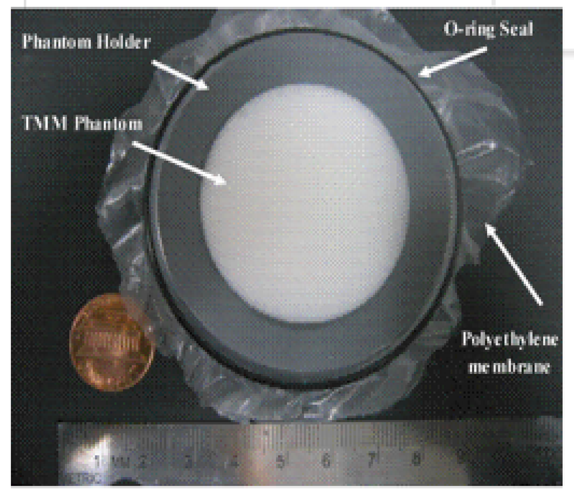
SUBMISSION NUMBER: Q180407

DATE OF SUBMISSION: 03/05/2019

https://www.fda.gov/media/128803/download

MDDT Ultrasound Phantom

TMM Phantom

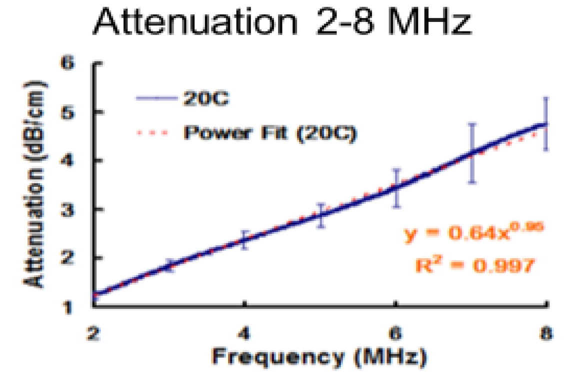


TMM Recipe

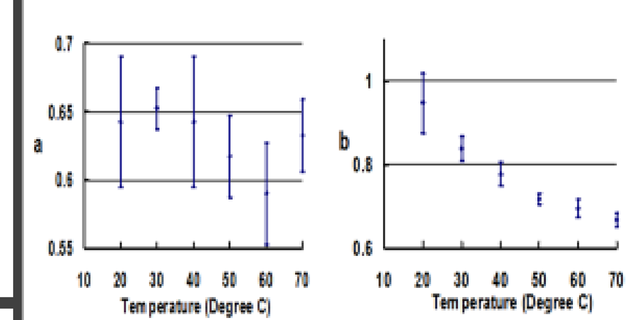
Materials	Function
Gellan Gum	Matrix
Degassed H_2O	Substrate
Calcium Chloride	Mechanical strength
Potassium Sorbate	Preservative
1-Propanol	Velocity
Aluminum oxide powder	Attenuation

As a HIFU developmental tool, a tissue phantom should produce consistent and representative thermal responses under various sonication conditions

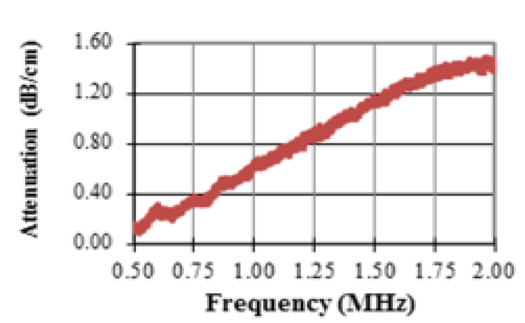
Attenuation 2-8 MHz

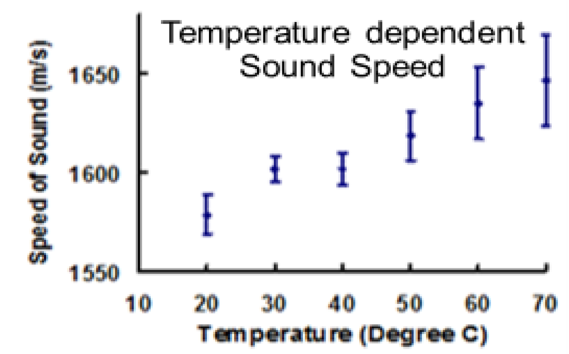


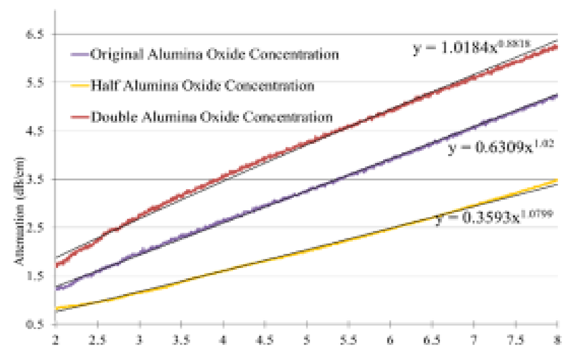
Temperature-dependent Attenuation = a f^b dB/cm



Attenuation 0.5-2 MHz





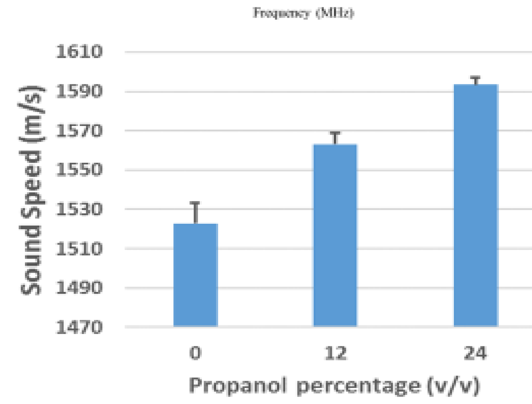


Tunability of TMM

Recipe can be modified to vary acoustic properties for different ultrasound applications

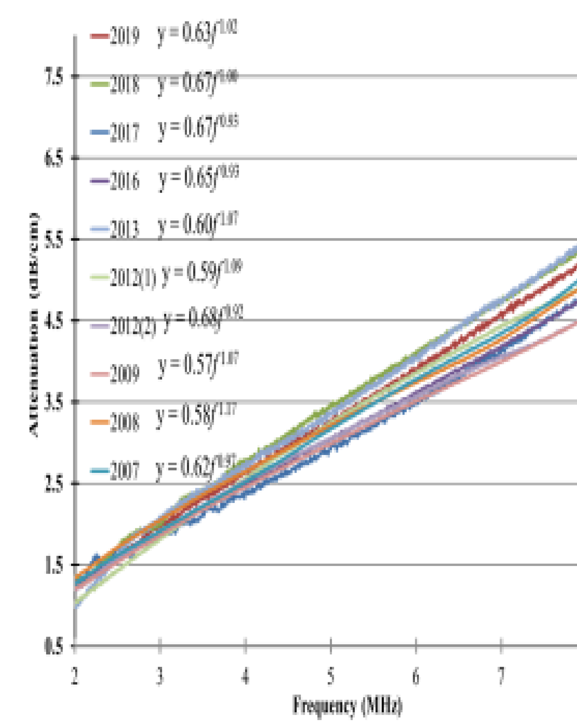
Sound speed can be modulated from 1522 to 1593 m/s by increasing the 1-propanol concentration from 0% to 24%

Attenuation ($0.63f^{1.02}$) can be varied by reducing or doubling the alumina oxide concentration to $0.36f^{1.08}$ or $1.02f^{0.88}$



MDDT Ultrasound Phantom

Manufacturing/User Variations



Developed in 2007 and characterized and tested under various HITU studies

King et al. 2011, Dunmire et al. 2013

Used to investigate thermally significant HITU-induced cavitation activity and corresponding temperature variations with ex vivo swine muscle

Maruvada et al. 2011

Demonstrated reasonable agreement between HITU numerical simulation and experimental temperature measurement

Maruvada et al. 2015

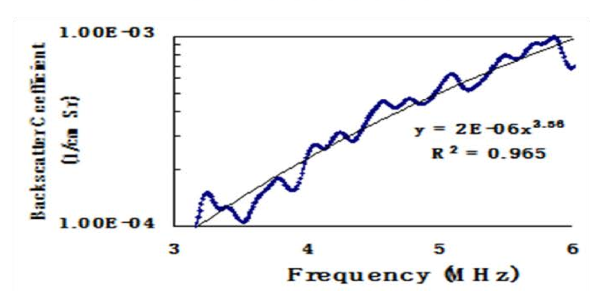
Employed as an integrated phantom testbed (blood flow, bone mimic and thermocouples) to evaluate an image-guided non-invasive HITU cuff system for automatic thermal coagulation of emergent internal bleeding injury (funded by DARPA)

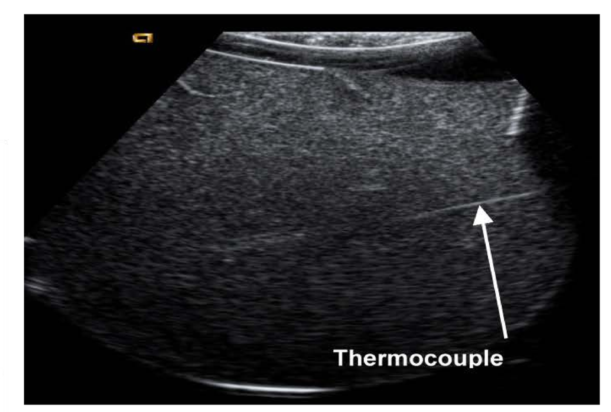
Sekins et al. 2015

Used to facilitate therapeutic ultrasound dosimetry and clinical studies, including ultrasound hyperthermia IR thermography, HITU nanoparticle enhancement, HITU ethanol ablation and ultrasound droplet imaging (University of Cincinnati and University of North Carolina)

Giridhar et al. 2012, Dibaji et al. 2014, Arena 2015

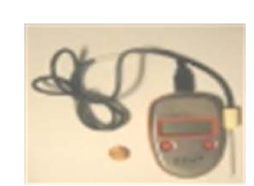
Backscatter Coefficient



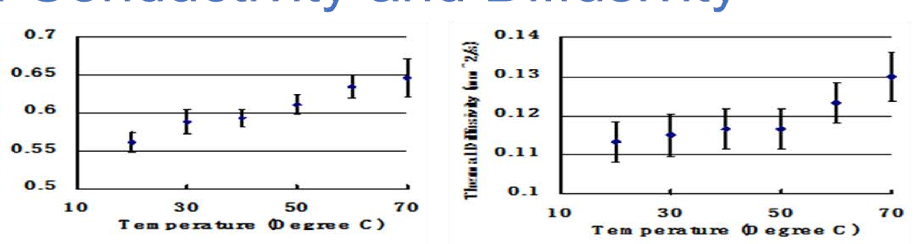


Imaging capability will facilitate phantom treatment planning and monitoring for ultrasound-guided HITU device testing

Thermal Conductivity and Diffusivity



KD-2 thermal property analyzer

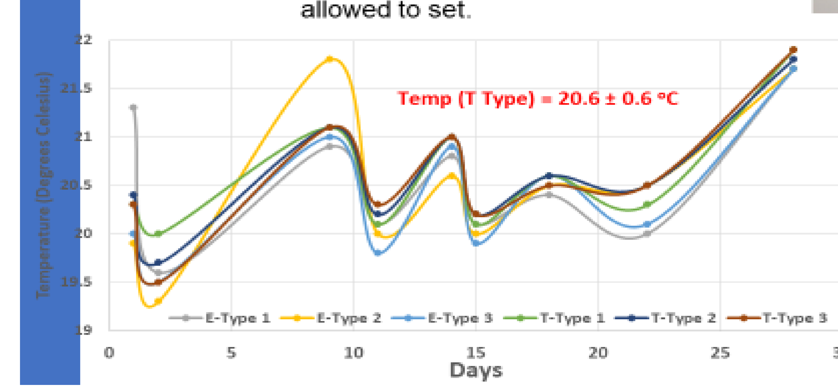


2.3 MHz HITU transducer was used to test the TMM for consistent thermal response.

8-cm diameter cylindrical mold was constructed with an opening for a B-mode imaging probe to monitor HITU sonication.

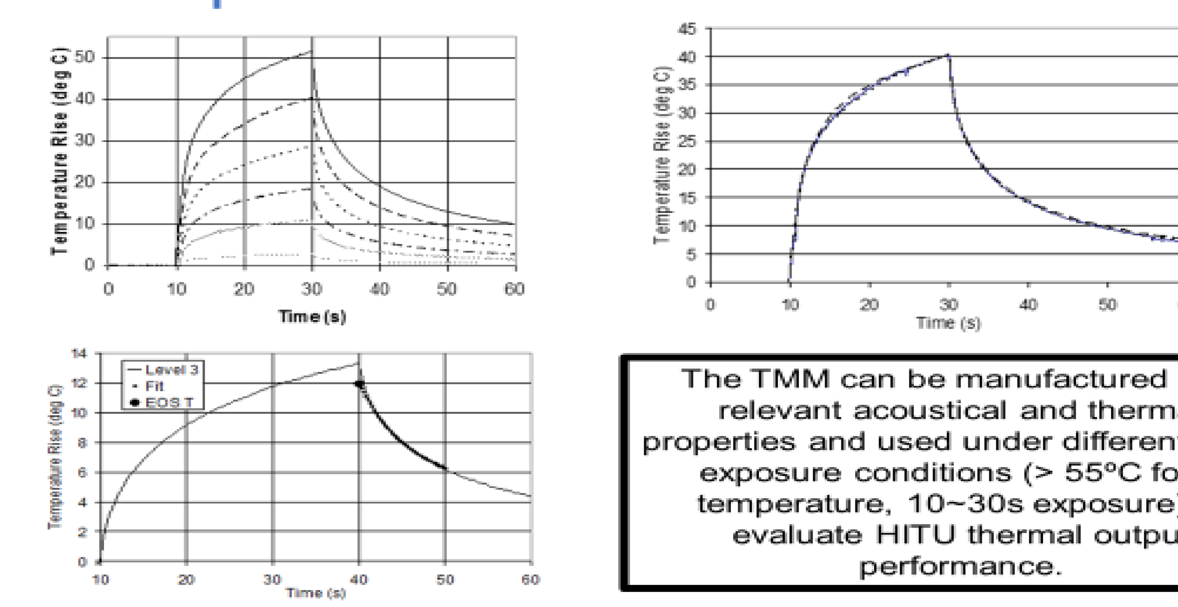
A 75-µm-diameter bare wire thermocouple was affixed through the center of the mold. The TMM mold with thermocouple was cleaned by boiling in degassed water with surfactant for 20 minutes to remove cavitation nuclei.

Once prepared, heated TMM was immediately poured into the mold (with thermocouple) and allowed to set.



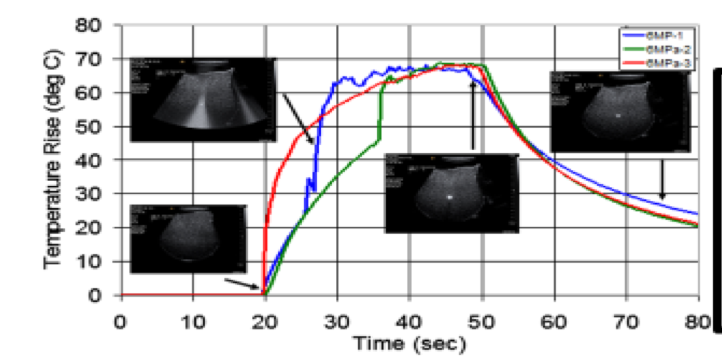
HIFU Temperature Measurements

Temperature Measurements



The TMM can be manufactured with relevant acoustical and thermal properties and used under different HITU exposure conditions (> 55°C focal temperature, 10~30s exposure) to evaluate HITU thermal output performance.

Temperature and Cavitation



TMM phantom captured the aggregate thermal effects under the influence of cavitation artifacts, which should be avoided during thermal performance testing.

MDDT Phantom Properties

Physical Properties (20°C)	TMM phantom	Soft tissue range
Acoustic Attenuation, dB/cm	**$0.64 f^{0.95}$**	$(0.5\text{-}1.0) f^{(0.9\text{-}1.44)}$
Speed of sound, m/s	**1579±17**	1510 ~ 1590
Nonlinear Parameter B/A	**8.2±1.3**	7.5 – 9.7
Acoustic Impedance, kg m^{-2} s^{-1}	**1.62±0.2**	1.6-1.7
Backscatter Coefficient, $cm^{-1}Sr^{-1}$	**2.2 e^{-4} @3.5 MHz**	2.0 e^{-3} @3.5 MHz
Thermal Diffusivity, mm^2s^{-1}	**0.11±0.005**	0.10 ~ 0.15
Thermal Conductivity, Wm^{-1} °C^{-1}	**0.56±0.013**	0.47 ~ 0.57
Density, g/cm^3	**1.027±0.019**	1.0 ~ 1.07

Conclusion

- With similar physical properties to non-fatty soft tissues, this TMM provides a convenient *in vitro* bench testing tool for evaluating exposimetry performance, validating numerical models, and evaluating HITU thermal safety
- The TMM with characterized physical properties can accelerate the time to develop and evaluate output performance of clinical TU devices
- It will provide an ultrasound bench testing phantom platform and facilitate animal study designs.
- Thermal safety for a non-ablation ultrasound device, such as for drug delivery and neuro-modulation treatments, can also be tested using the proposed TMM
- The TMM can be manufactured conveniently with desired acoustical and thermal properties and measure repeatable temperature rise under TU exposure conditions (> 55ºC, 10-30 s exposure)