"A novel, scalable, isothermal method for nano-emulsion formation"
Srikanth Kakumanu¹, Mathieu Schmitt², Xiaoyin He¹, Carl Beckett¹, and James Laugharn¹

¹Covaris Incorporated, Woburn, MA, 01801, USA
²Novagali Pharma, Genavenir IV, F-91058 Evry cedex, France.

ABSTRACT SUMMARY
Nanoemulsions are a very effective method for encapsulation and biological delivery of active ingredients (1). Current methods for the formation of nanoemulsions include high shear force methods such as Microfluidizers, and low energy methods such as Self Assembling Nano Emulsions (SANE) (1-4). This paper studies the results of forming nanoemulsions through the use of Focused-ultrasonication including the ability to form stable, monodisperse nanoemulsions. Findings show that the use of focused acoustical energy is very effective to form nanoemulsions across a range of sample volumes from under 0.50ml through continuous process flow. The ability to formulate monodisperse, nanoemulsions, with average particle sizes down to 20nm was demonstrated with a poly-dispersity index below 0.100. All results were achieved in very fast process times and with sample temperatures held below room temperature in all cases. Samples ranging from <1ml to continuous flow stream were prepared.

INTRODUCTION
Adaptive Focused Acoustics (AFA) has proven technical advantages in several biological based applications including DNA shearing, tissue homogenization, and cell lysis and disruption (2-4). The ability to apply a controlled mechanical energy at the molecular solvent boundary layer has begun to influence its capability in the formulation of nano-emulsions of biological, pharmaceutical, and any thermal sensitive (degeneration) materials. Several characteristics has brought attention to the technology including: fast and convenient operation, isothermal processing eliminating molecular damage due to overheating, high reproducibility, self contained, non contact processing, and the ability to scale from sample volumes of 0.15ml up through Pilot Scale. This is only optional technology feasible to work at lower Volumes during the developmental phase, which saves lot of expensive ingredients.

EXPERIMENTAL METHODS
An emulsion formulation of 1:1 Tween 80 and rice bran oil was prepared to create the basis for a 2ml nanoemulsion blank.

The formulation was subjected to focused-ultrasonic processing of 300W for 6 seconds using an AFA-based S220x instrument from Covaris, Inc. Woburn, Massachusetts. Acoustic processing conditions were varied to show the effect on particle formation. The sample temperatures were monitored over a range of power inputs to determine max sample temperature rise. Finally, a continuous process stream was created via real time injection and mixing of the components into the active acoustic field.
Average particle size as a function of acoustic power input showing a correlation between power level and particle size/distribution.

Average particle size and distribution as a function of acoustic process time, showing a plateau after which additional processing no longer affects particle size.

A continuous process system was configured to enable a real time continuous stream of emulsion. Temperatures were measured at the inlet and outlet of the system:

In all cases the maximum sample temperature was below 17°C:

Focused-ultrasonic acoustics can be a very effective technology to aid in the formulation of nanoemulsions. The ability to control a high power density, delivered to the sample in a completely contained and non contact manner, combined with the precise thermal control during the process, offers an attractive combination of benefits when compared to existing known technologies. AFA brings to scientist an innovative, robust and easily scalable process to formulate active ingredients degraded under physical and/or thermal stress as nano-emulsions.

REFERENCES