

## Development of a Temperature-Recording Vaginal Ring for Monitoring User Adherence

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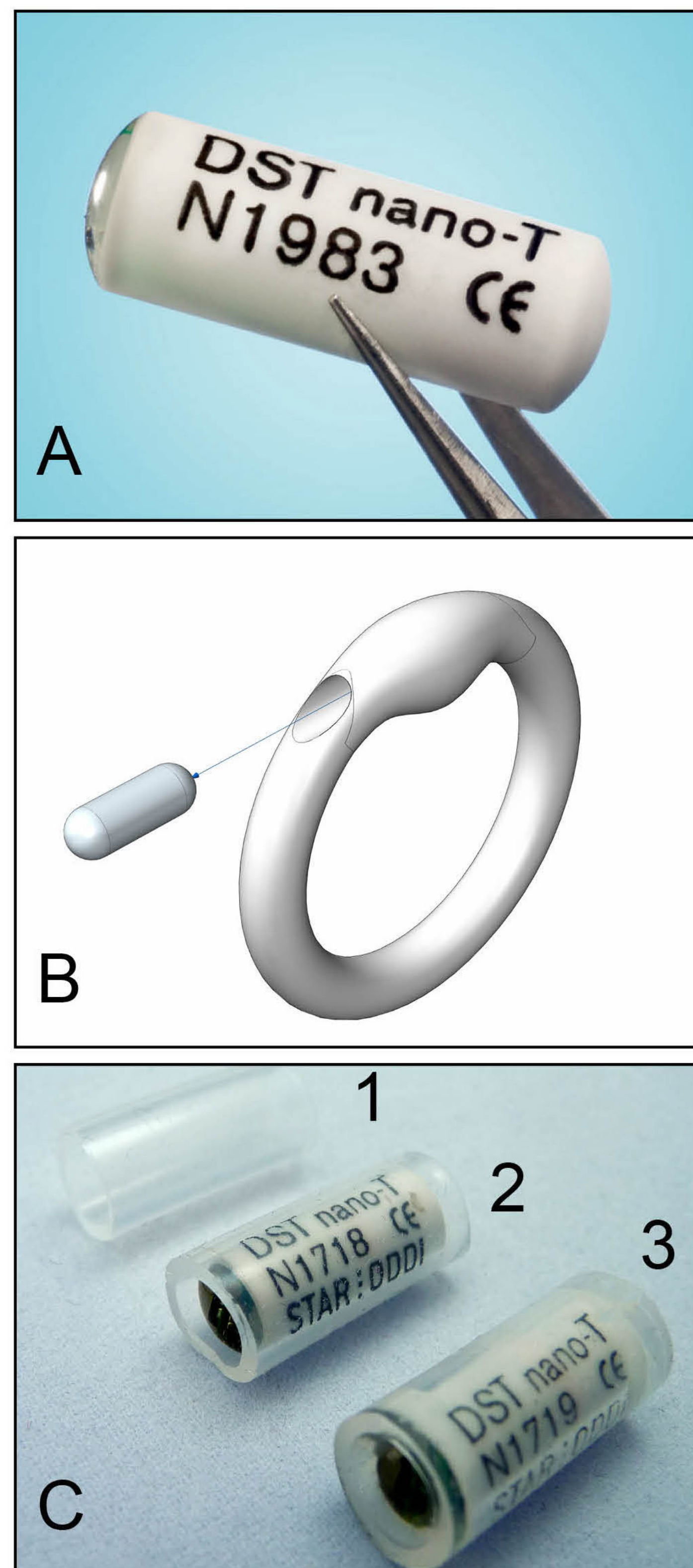
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# A TEMPERATURE-RECORDING VAGINAL RING FOR MONITORING USER ADHERENCE

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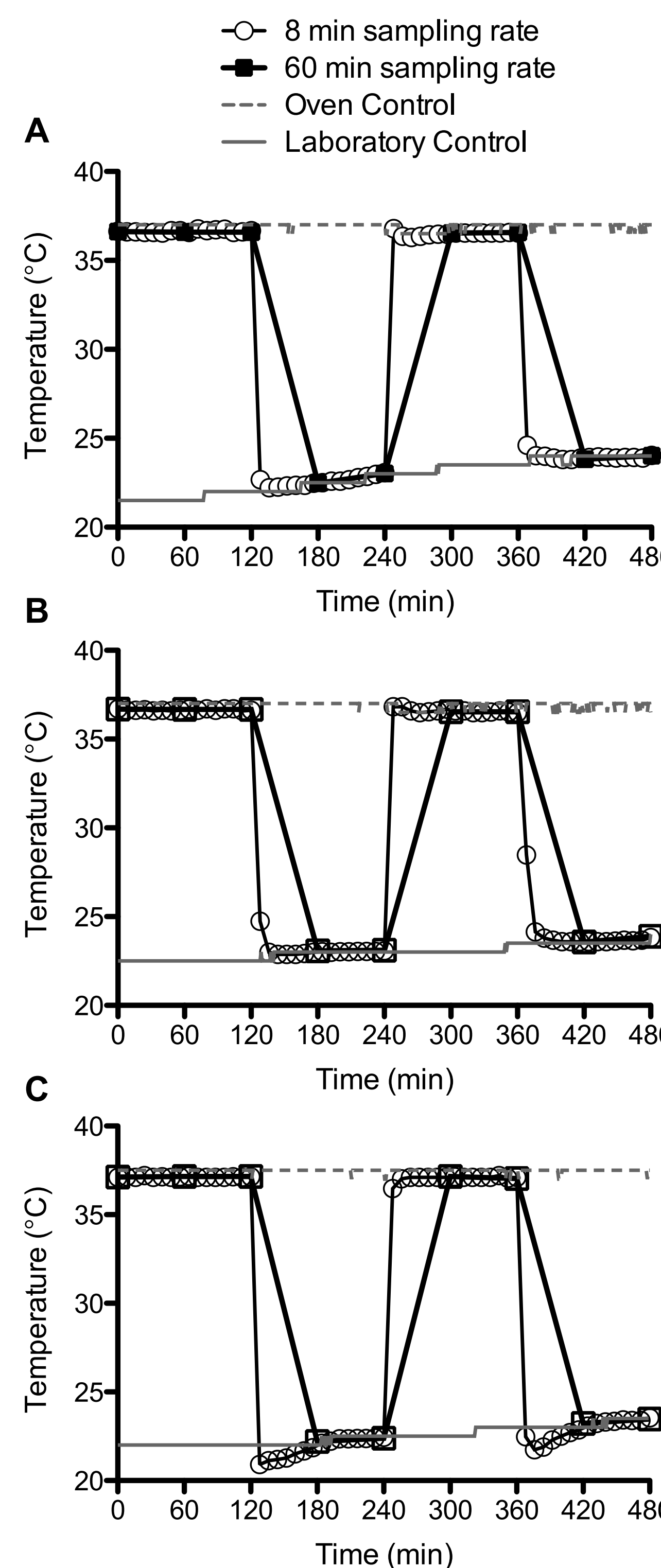
One of the major challenges for late-stage clinical trials in the HIV microbicide field is the accurate (and preferably quantitative) measurement of adherence. Methods for measuring adherence can be divided into two categories. Direct measures of adherence, also known as 'biomarkers', are substances or effects whose absence/presence indicates that a biological or pharmacological process has occurred. Indirect measures of adherence include 'objective measures' and 'self-report measures', both reliant on the observations or reports of clinicians, trial participants, or others.

The relatively large size of vaginal rings (particularly silicone elastomer rings, Fig. 1B) compared with more conventional vaginal dosage forms, their method of manufacture, and their non-degradable properties permit the incorporation of a miniature temperature-recording device into the ring body. Assuming (i) the embedded temperature-recording device can accurately and periodically record environmental temperature, (ii) internal vaginal temperature is significantly different from external ambient temperature, and (iii) the vaginal ring is returned to the clinic after use, it may be possible to use such a ring to accurately monitor user adherence. Here, we report that DST nano-T temperature loggers (Fig. 1A, Star-Oddi) embedded within model silicone elastomer vaginal rings (Fig. 1C) can accurately and continuously record environmental temperature and determine insertion and removal events, both in vitro (Figs. 2 & 3) and when administered vaginally to cynomolgus macaques (Fig. 4).

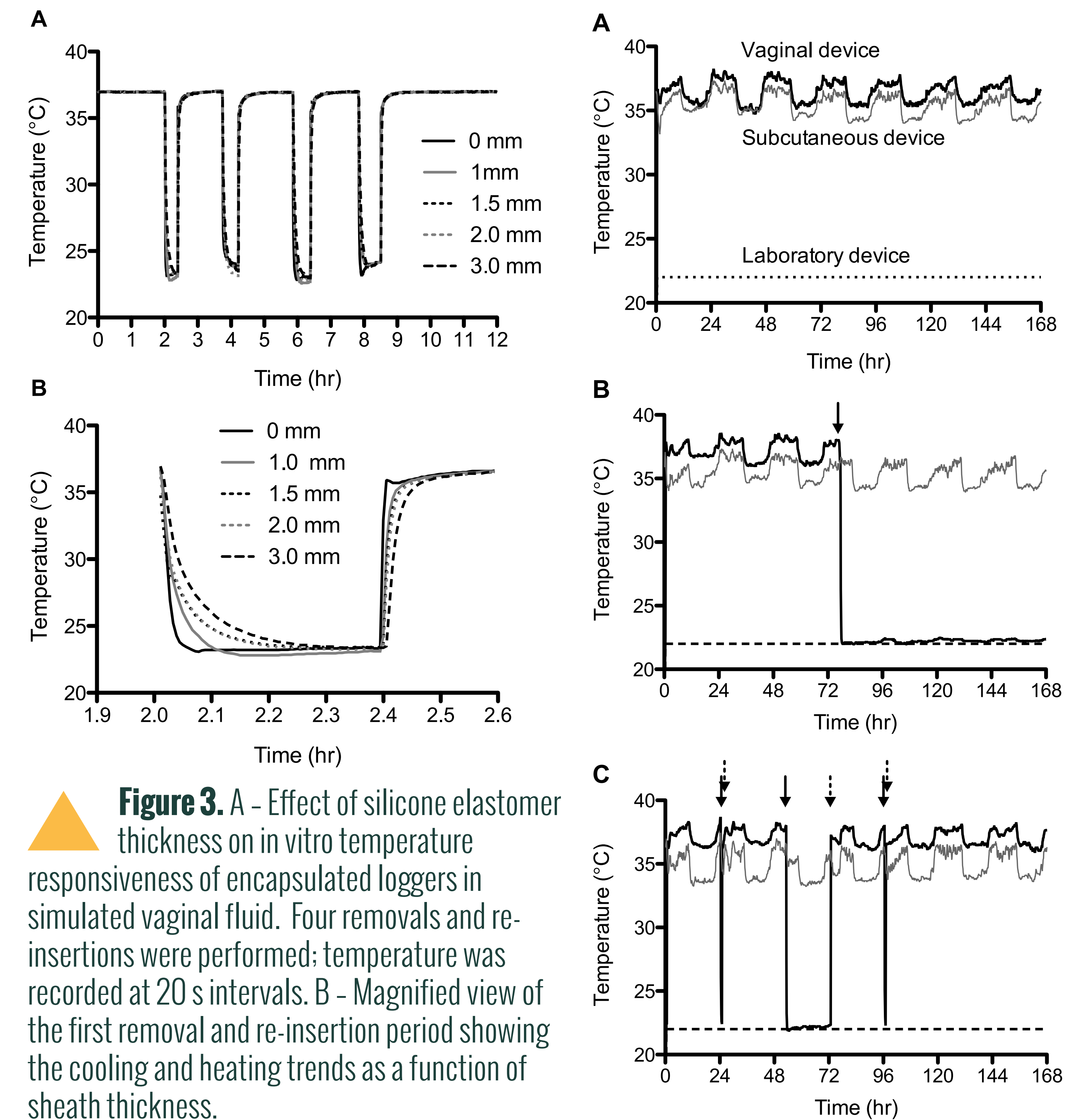
Temperature loggers (as supplied, encapsulated in silicone tubing, or encapsulated and placed in simulated vaginal fluid) were responsive to changes in temperature resulting from removal from and re-insertion into a laboratory incubator (Fig. 2). The 8 min sampling interval more accurately defined the removal and re-insertion events compared with a 60 min interval. An evaporative cooling effect was observed in the simulated vaginal fluid experiment (Fig. 2C). The thickness of the silicone elastomer sheath surrounding the temperature logger also affected the responsiveness to temperature changes (Fig. 3), although removal and re-insertion times were still readily determined.

In macaques, a regular diurnal temperature pattern was observed for both vaginal and subcutaneous loggers (Fig. 4), although vaginal temperatures were consistently 1-2 °C higher than subcutaneous temperatures. Vaginal device removal and re-insertion events were clearly detected by the silicone elastomer encapsulated loggers (Fig. 4B and 4C). A Phase 1 human clinical study is now planned.

**Figure 1.** A - DST nano-T temperature logger. B - Silicone elastomer vaginal ring with logger inserted. C - Steps involved in encapsulating the logger in silicone tubing for testing in macaques.



**Figure 2.** In vitro testing of temperature loggers. A - as supplied. B - sealed in silicone elastomer tubing. C - sealed in silicone elastomer tubing and placed in simulated vaginal fluid.



**Figure 3.** A - Effect of silicone elastomer thickness on in vitro temperature responsiveness of encapsulated loggers in simulated vaginal fluid. Four removals and re-insertions were performed: temperature was recorded at 20 s intervals. B - Magnified view of the first removal and re-insertion period showing the cooling and heating trends as a function of sheath thickness.

**Figure 4.** Temperature responses vs time for vaginally and subcutaneously administered temperature loggers in cynomolgus macaques. Each graph shows data for a single animal. Solid and dashed arrows indicate removal and re-insertion of the vaginal device, respectively. Dashed line indicates laboratory temperature (~22 °C). A - vaginal device worn continuously for 7 days. B - vaginal device removed after 3 days. C - vaginal device removed and reinserted on three separate occasions (for 30 min, 19 h, and 30 min) during the 7-day period.