

## Medtronic comments on Clinical Assessment of Rate-Adaptive Pacemakers

(April 4, 2000 Circulatory Systems Devices Panel)

FDA has published a draft guidance "Evidence Models for the Least Burdensome Means to Market" on September 1, 1999. In this document, FDA recommends following a two-stage/question model in order to determine the most appropriate and least burdensome method for evaluating medical devices. Medtronic's comments on the above topic follow this model.

***Question 1. Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population.***

Points that should be considered when evaluating this question include:

- Indications for the device (i.e., the target population of patients)
- The technology and mode of action for the device and if these items are well accepted/understood

### Regarding Indications

Medtronic contends that the indications for bradycardia pacing have been and are well understood. In fact, FDA has created a labeling template for bradycardia pacemakers specifying the recommended indications and contraindications for these devices. Pacing manufacturers have essentially adopted the recommendations from this template. Therefore, as the target population for bradycardia rate responsive pacing is well established, the remaining salient issue is rate responsive technology and existing clinical data.

### Regarding Technology and Applicability of Current Data

As mentioned in the FDA panel package contents, rate responsive pacing has been in existence from an atrial tracking perspective since the early 1980's. Sensor driven rate response occurred with the advent of the Medtronic Activitrac device approved in 1986. Over the last 14 years, different types of sensors have been exhaustively studied and approved for use in rate responsive pacing.

Medtronic contends that the current technologies used for rate response (piezoelectric crystal, MV sensor, accelerometer, QT interval, etc.) have been studied and are understood by industry, FDA, and physicians as to their mode of action and effectiveness.

Given this, and the "least burdensome" approach to "Rely on non-clinical testing for decision-making when possible", Medtronic believes that for current sensor technology, bench data can be used to prove effectiveness of rate response. Specifically, as FDA indicates, strap on testing of piezoelectric or accelerometer devices correlate well with implanted devices. Strap on testing can be further extrapolated to more controlled bench

top "shaker" table testing which characterizes response of a sensor over a greater variety of inputs. FDA approved devices can be placed in such a bench testing environment and their sensor and rate response can be evaluated and compared to new devices employing similar sensor technology. Furthermore, combinations of already approved sensor technology can also be evaluated in this same fashion.

Medtronic contends that clinical data is only necessary to evaluate rate response effectiveness when completely new technologies are involved.

***Question 2. What is the most appropriate and reasonable way to obtain these data?***

Medtronic believes that the clinical data required to prove the effectiveness of rate response depends on the claim a firm wants to make for their device/technology.

Over the last 2+ years, FDA has standardized the way pacemaker manufacturers analyze rate response data to support a generally accepted claim. This claim is stated DCRND's document "Suggested CAEP Analysis Plan". This document outlines the claim, study design, endpoints, etc. which have been used by manufacturers in the last two years to obtain the claim listed in the document.

For new sensor technologies, Medtronic believes that the least burdensome clinical evaluation for rate response effectiveness is based on DCRND's document. Specifically, approximately 30 patients, followed for 1 month's time should undergo a validated exercise protocol (validated meaning there is a known correlation between the exercise stages and Metabolic Equivalents). Patients should be programmed to 85% of their age predicted maximum (220-age) as recommended by Wilkoff, et. al. and should achieve maximal exertion in order to fit the Wilkoff model. Sensor indicated rate at each stage can then be compared to the expected rate and normalized via the Kay method. The 95% confidence interval on the mean slope should then be greater than 0.65 and less than 1.35 in order to state the claim that is presented in the DCRND document. Essentially, this method has been FDA's guidance over the last 2 years. This approach has the benefit of a standardized method that involves minimal patient hardship and time while providing well-accepted data.

The panel package referenced a concern regarding the inclusion criteria for patients in such a study, commenting on the definition of chronotropic incompetence. However, by using sensor indicated rate instead of patient actual rate, and by not relying on physiologic measurements for an end point but an accepted rate response model, the need to have strictly defined inclusion criteria with respect to chronotropic incompetence is not necessary. Furthermore, by evaluating the sensor indicated rate and not the patients' intrinsic rate, an increasing and proportional response of the device to workload can be established demonstrating appropriate response. This knowledge is sufficient to approve a rate response product for use in the general population.

Additionally burdensome study designs referenced in the panel pack (e.g. randomized controlled, single-arm crossover) may be appropriate in cases where company's wish to

pursue claims beyond those listed in the DCRND document. For example, a manufacturer may wish to show that their sensor technology reduces symptomatic high rate pacing, or a manufacturer may wish to demonstrate greater physiologic benefit via measurement of greater oxygen uptake – these may be cases where randomized and/or crossover designs are appropriate as they are to make claims beyond the basic claim of providing "...Rate Response similar to the predicted Wilkoff model..."

### Conclusion

The questions placed before the panel regarding the clinical evaluation of rate responsive pacing appears to encourage clinical study designs that are more burdensome than those currently accepted today and encouraged via FDA's own draft guidance document. This appears contrary to the spirit of least burdensome, especially considering the technology and issues in question are 14+ years old. Using FDA's least burdensome guidance, Medtronic suggests that current technologies/sensors and combinations of these technologies can actually be evaluated to demonstrate effectiveness via bench models/testing. For new technologies, Medtronic suggests that the least burdensome clinical evaluation be similar to the methods and analysis provided in DCRND's draft guidance. If a manufacturer seeks additional claims, more complex studies may be necessary based on the specific claims desired.

### References

- Wilkoff BL, J Corey, and G Blackburn, "A Mathematical Model of the Cardiac Chronotropic Response to Exercise" **J Electrophysiology**. 1989;3(3):176-180
- Pacing and Electrophysiology Group, DCRND, ODE, CDRH, "Suggested CAEP Analysis Plan" 12/02/98
- CDRH, ODE "Guidance for Industry and FDA reviewers on Evidence Models for the Least Burdensome Means to Market" Draft Guidance published for review September 1, 1999
- Kay GN, "Quantitation of Chronotropic Response: Comparison Methods for Rate-Modulating Permanent Pacemakers" **J Am Coll Cardiol** 1992;20:1533-41