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SUMMARY

It appears that the FDA has reservations about biventricular pacing technology and wants to see more convincing data. In this environment, requests for patient expanded access to trial devices are on-hold, and Guidant's ability to get approval of the Contak-CD without an additional clinical trial is questionable. Much will hinge on the outcome of the March 2002 FDA Advisory Panel on Medtronic's InSync-ICD.

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BiVentricular Pacing Update

Interviews with electrophysiologists and FDA officials indicate that the March 5, 2002, FDA Advisory Committee may be a critical meeting. The panel is expected to take up only the Medtronic InSync-ICD, not the Guidant Contak-CD, but the outcome of the panel meeting is likely to affect Guidant and St. Jude as well as Medtronic.

A knowledgeable source said, "I heard Guidant was turned down by the FDA for expanded access to the Contak-CD. Medtronic put in a request to the FDA for an extension on continued access to the InSync-ICD, and is expecting a decision soon, but I'm not sure they will get it since Guidant was turned down. The Medtronic delay has been a problem for us because we had patients scheduled to get the device. I heard the FDA was not as impressed with the InSync data as it might have been either, so I think the agency wants to see the panel response in March to the InSync-ICD data before making a decision, and I doubt the agency will act on anything until then."

Guidant officials have indicated that failure to be included on the panel agenda does not preclude approval, suggesting that a panel may not be required for the Contak-CD. One expert said, "The Contak-CD trial ran into some problems because there were too many questions trying to be answered by that single trial. If you look at sickest patients and compare them to the patients in the (Medtronic) InSync trial, it is an overlay of results. These are identical devices, and the Contak-CD is widely used in Europe. I am very convinced that there is no difference between Contak-CD and InSync when you look at the same subgroups of patients. One of the other problems in Contak-CD was that some of the patients that qualified had not been on three months of beta blocker therapy yet or not on maximum drug therapy yet, and they got better with beta blockers and fell out of the trial."

However, it is clear that the FDA wants more data on the Contak-CD. A source said, "The FDA has asked for another trial of 200-300 people." Will the company be required to do another trial? Perhaps not, some sources say. An expert said, "Personally, I don't think Guidant will need another trial. I think it can rework the data to the satisfaction of the FDA."

One suggestion that has emerged is that Guidant may be able to stop the COMPANION trial early and use data from that trial instead. A source said, "There is an ongoing mortality trial – COMPANION – that is asking a very important question, and it has the same enrollment as Contak-CD: Class III-IV heart failure. COMPANION is looking at whether biventricular pacing by itself or with an ICD (defibrillator) will make a difference in mortality, not just how patients feel. It is like a second trial, looking at the same group of patients."

Stopping COMPANION early (breaking it) may be less of a problem if the MADIT-2 trial leads to a change in ICD labeling, an expert suggested. In fact, he predicted that the MADIT-2 trial may make it difficult if not impossible to continue the COMPANION trial, "If – and I emphasize if – the FDA changes the

indications for ICDs as a result of MADIT-2, a large number of the kind of people you would normally try to put in COMPANION, will meet MADIT-2 criteria, and that will create a real ethical dilemma for investigators. How could we then give patients something without an ICD? It would be a very, very difficult ethical problem. If ICDs are approved for MADIT-2 indications, I probably will not enter people with MADIT-2 indications into COMPANION, which puts the COMPANION trial in great jeopardy. So, if the mortality trial wouldn't finish for maybe 10 years, if at all, personally I would stop the trial. You would still have a placebo group and could look at symptomology, hospitalizations, etc."

Other doctors were less enthusiastic about the idea of breaking the COMPANION trial. A source said, "Breaking COMPANION would be horrible because we are well into the protocol and we wouldn't get the mortality data. It would be really sad. How can the data help Guidant? It is another data set, but I don't think it will make Guidant's position better!"

The FDA may not be receptive to stopping COMPANION early so the data can be used to bolster the Contak-CD filing, though officials would not rule the possibility out entirely. One official, speaking in general terms about the pooling of data from two trials like these, said, "My gut level response is that the company can't do that. Each trial generally has a slightly different population. If the patient populations aren't exactly the same, I don't think you could combine them. And the studies are going to be designed a little differently, so the results they would find would be different. But it is possible that we would allow it at times." Another FDA official said, "There are circumstances where pooling might be allowed – if the indications and outcomes were the same. It depends on what you are looking to show with pooling. There could be circumstances where it is appropriate, but it has to be evaluated on a case-by-case basis, and the onus of establishing the appropriateness of doing it falls to the applicant. I am always willing to listen to arguments or discussion, but the circumstances have to be just so. Being the conservative person I am, I would be less inclined to support such an approach, but that doesn't mean I wouldn't let the company make the argument. Our regulations say companies need to provide scientific data to assure safety and efficacy, and if a company can make the case that it is valid scientifically (to break the trial) and with that data it can prove safety and efficacy, then I am beholden to hear the argument."

Among the issues the FDA would look at in any pooled data situation are:

► Is all the pooled data from the same manufacturer? An FDA official said, "You can't take data from one manufacturer and use it to get a product by another manufacturer approved. You can't pool data from two manufacturers. The likelihood of our approving that is minimal."

► What kind of statistical analysis is being used? The official said, "You would have to do a poolability analysis and show the populations in fact are the same. If you are collecting the data already and the same endpoints are part of the analysis, you may have a case to make…You might do a Bayesian analysis. For example if one study is 12 months long, but there is sequential data from 3, 6, 9 and 12 months, and a second study with another device is done for six months, with the device similar and the therapy the same, then you conceivably could do a Bayesian analysis to predict how the patients at six months will look at 12 months."

► How was the length of the trial to be cut short determined? Was it mandated by the FDA? The official said, "If the FDA approves a 12-month study, and the company later says it needs six-month data, you just can't cut it off at six months. If there was a need for 12-month data, then the trial has to continue for 12 months. Unless, of course, the company was just doing a 12-month study for fun. Then, it could cut the trial short."

Furthermore, a key source also was dubious that the FDA will act quickly on MADIT-2 labeling. He said, "The MADIT-2 data won't be presented at least until the American College of Cardiology meeting in March. It is at the New England Journal of Medicine now which may print it shortly – in February 2002 at the earliest. Until HCFA (CMS) pays for MADIT-2 labeling, it is a moot point, and HCFA won't do that until the FDA approves new labeling, and the FDA is not in a hurry. The FDA won't deal with MADIT-2 as fast as it did MADIT-1 because the FDA got negative flack for doing MADIT-1 so fast. My best guess is the FDA won't do this for a while because it is a really, really big deal because of the numbers of patients that will be involved. Let's say no earlier than February and probably more likely June for FDA labeling, and then HCFA has to act. Right now, HCFA has approved the technical fee for biventricular pacing but not professional fees, so we doctors are not getting paid for doing it, though we are trying to get paid under regular pacemaker implantation. Currently, there is neither a technical nor a professional fee approved for MADIT-2, so I suspect it will be sometime late this year before funding for MADIT-2 indications is available."

The implications of MADIT-2 are enormous sources said. One expert said, "MADIT-2 has the potential to double or even triple the ICD volume at our hospital. Two or three years ago, two-thirds of our devices were pacemakers and one-third were defibrillators. This year it is 55% pacemakers and 45% defibrillators. Next year, defibrillators will eclipse pace-makers, and I wouldn't be surprised if it is two-thirds defibrillators and one-third pacemakers. And that's not to say pacemakers will be down, just that defibrillator volume will go up. MADIT-2 has the potential to really blow ICD use open, but depends on HCFA (CMS). People don't understand that cardiac arrest is not a heart attack, that what they had was ventricular tachycardia, but we'll do a huge public information campaign soon to educate people."

St. Jude also reportedly is having some problems with its biventricular pacing trials. A source said the company is finding it difficult to randomize patients with InSync on the market, "St. Jude would have finished its trial in another month or two, but it has stopped randomizing patients. It petitioned the FDA to stop the randomization part of the trial, but the FDA said it wanted to see the Medtronic InSync-ICD data first." ♦