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MEDICAL DEVICES

Reengineering Device Translation Timelines

ON THE ROAD TO TRANSLATING MEDICAL IMPLANTS TO THE CLINIC, ONE MIGHT PASS several signs that warn, “Many hairpin curves ahead.” The hairpin curve, named for its resemblance to the bobby pin, exemplifies that one can see the clinical goal nearby while realizing the timelines to clinical use are much longer than they need to be. In this issue of *Science Translational Medicine*, Farra *et al.* (1) make good on the “hairpin image” by having trod the long, meandering pathway to clinical introduction of a new therapeutic implant that may, in the future, improve a patient’s quality of life. In this study, seven women were treated in the first clinical trial of a wirelessly controlled, microchip-based drug delivery system. The microchip represents more than 10 years of engineering design and development efforts to arrive at a programmable, implantable device for subcutaneous release of a therapeutic agent in discrete doses. The goal of such a device is to improve current chronic delivery methods, which often involve needles and repeated injections (for example, insulin for patients with diabetes). Not surprisingly, the proof-of-principle study of this controlled-release microchip was published in early 1999 (2).

The microchip created by Farra and colleagues has 20 microreservoirs programmed to release 20 doses of drug. Several engineering design advances were necessary to ensure the microchip technology was “ready” and safe for testing in humans: (i) hermetic sealing of each drug-filled reservoir; (ii) electrothermal ablation of reservoir membranes to release the drug; and (iii) aseptic filling and lyophilization of the drug delivered to the reservoirs. Also, as is well known, subcutaneously placed medical implants become biologically encapsulated in fibrous tissue, which may influence drug delivery pharmacokinetics. This consideration was carefully addressed and analyzed in the study (1).

Microchips were implanted in seven women for 103 days. The implant was used to deliver 19 daily doses of microgram quantities of an antiosteoporosis drug during days 57 through 75. Farra *et al.* successfully showed that this microchip-based drug delivery device provided pharmacokinetic profiles similar to subcutaneous injections—even with the fibrous tissue capsule. Although drug efficacy was not examined for this particular trial, bone marker evaluation indicated that daily release of the drug increased bone formation. Moreover, during the trial, quality-of-life surveys were taken four times. Survey results demonstrated that the majority of patients recounted they often forgot they had the implant and that they would agree to subsequent surgery to implant a “fresh” device.

Every medical diagnostic and therapeutic product or procedure is an outcome of both the scientific method and the engineering design process. This article by Farra *et al.* (1) affords us the opportunity to highlight some of the many factors inherent in translating a new technology to a clinical setting. In this report, the scientific method and the engineering design method were in equilibrium. For the scientific method, the study helped to formulate the hypothesis for more definitive, later-phase clinical trials. The engineering process gained data to better define the system requirements that are needed for these future trials. On balance, the results of this clinical study provide verification of the functionality limits of the implant design and of the quality of the device itself.

Although the new work documents the first-in-human trial of this implantable device (1), many translational questions and requirements remain. The clinical therapeutic goal has not yet been fully defined, so the microchip requirements are incomplete. The reliability and durability of the microchip have not been established; this, too, has a long timeline that relates directly to each defined therapeutic strategy. In the Farra *et al.* study, the device failed in one patient (an eighth patient, not included in their analysis), and the manufacturing process yielded only one device with all 20 reservoirs of drug. Nevertheless, all doses present were released from the seven devices. Several years are still needed to bring this technology to approval by the U.S. Food and Drug Administration (FDA) and to the clinical promise reflected in this pilot study.

There are several essential parallel pathways to translate a new medical product or process to clinical use: funding and financing, research and development, regulation and payment,

design controls, clinical trials, facilities and manufacturing, intellectual property, and marketing and sales. The microchip-based device (1, 2) has been making progress along each pathway for more than a decade, and—as with all potential medical devices—will benefit from considerable innovation in all of these areas to shorten the timeline to routine clinical application. For example, decreasing the timeline of some clinical translational process challenges is a stated goal of the U.S. National Institutes of Health Clinical and Translational Science Awardees (CTSA) (3). Champions of Change were appointed to direct and implement process improvements at more than 90% of the CTSA clinical sites (4). To improve clinical trial recruitment in the CTSA-driven and other approved trials, a nationwide patient recruitment program called ResearchMatch has been established (<http://www.researchmatch.org>) and has helped register patients for more than 250 clinical studies to date. In fact, the first in-human study described by Farra *et al.* (1) was conducted in Denmark by a contract research organization, Center for Clinical and Basic Research, whose mission is to “speed up clinical trials” (<http://www.ccb.com/en>) by recruiting patients more quickly and in greater numbers at its 16 international sites, as compared with single investigator sites.

The mission of *Science Translational Medicine* was reemphasized by Elazer Edelman and Garret FitzGerald as they assumed their roles as co-chief scientific advisors to the journal in 2011 (5). This paper by Farra and coauthors fits well within the journal’s mission because it reports on the results of a promising medical implant drug delivery system in a small clinical study (1). Experience suggests that this technology must still negotiate several years of translational hurdles if, in fact, it becomes part of our clinical armamentarium. For example, the Gliadel implantable wafer developed by Brem and colleagues received FDA approval for brain cancer treatment after 17 years of science, engineering, and development (<http://web.mit.edu/newsoffice/1996/wafer-1002.html>), as well as a pivotal phase III trial in 222 glioma patients (6). Innovations in translational medicine, such as the new FDA Centers for Excellence in Regulatory Science and Innovation located at the University of Maryland and Georgetown University, could reduce the timeline of the translational pathways and could, in turn, benefit patients earlier and help stabilize health care costs. For Farra, Langer, and colleagues, the hairpin road to the clinic might be long and winding, but a versatile implantable device that capitalizes on the microchip approach for controlled drug delivery will be well worth the wait for patients with chronic diseases.

—John T. Watson

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