Advancing the Field of Ophthalmology

Is the European process superior to that of the United States?

BY JORGE L. ALIÓ, MD, PHD, FEBO

During the past decades, the innovations in ophthalmology have been a highlight in all of medicine. The development of modern techniques for cataract removal and IOL implantation, new vitreoretinal surgical and medical therapies, the evolution of refractive surgery—both corneal and intraocular—and more recently, corneal collagen cross-linking and new surgical approaches to glaucoma are promoting ophthalmology to a higher level than ever before.

> "Traditionally, the United States has been considered a relatively hostile or at least difficult environment for medical innovators due to the many limitations that are imposed by the FDA."

THE PROCESS OF INNOVATION

Innovation has a process. First, a creative idea and a creator capable of transforming it into a real application are needed. Next, the idea has to be put into action. Eventually, a clinical trial should demonstrate (or not) that the new method works for the purpose for which it has been created, and the trial should investigate the potential limitations, complications, or insufficiencies of the treatment for the control of the disease or anomaly for which it has been created.

Traditionally, the United States has been considered a relatively hostile or at least difficult environment for medical innovators due to the many limitations that are imposed by the FDA. When I lived in the United

ARE CHANGES TO THE CE MARKING PROCESS IMMINENT?

Although the European Commission's new regulations will still be somewhat innovation friendly, they may slow down the regulatory pathway.

BY ARTHUR CUMMINGS, MB CHB, FCS(SA), MMED(OPHTH), FRCS(EDIN)

When talking with US colleagues about ophthalmic devices and new technology, the FDA is often referred to as "Foreign Development Assured" or "For Development Abroad" and many variations on the theme. Reference is always made to how we are so fortunate in Europe not to have the FDA and hence can gain access to new technology that allows us to better treat our patients.

Meanwhile, the French breast implant manufacturer Poly Implant Prothèse, better known as PIP, was found guilty of selling implants containing industrial-grade silicone. This event has almost single-handedly been responsible for the changes occurring in Europe's system. More regulations will be enforced that will soon remove most of the advantages that Europe currently enjoys compared with the United States in terms of the time it takes to get a device to market.

ARE CHANGES TO THE CE MARKING PROCESS IMMINENT? (*CONTINUED*)

What are the changes in the pipeline, and when will they happen?

EUROPEAN COMMISSION'S PROPOSALS

Although preserving the innovation-friendly approach, the commission would like to revise the regulatory framework to ensure health and safety and smooth functioning of these pathways. The commission has been considering how to impose tighter controls on manufacturers of medical devices and notified bodies.[1] A notified body is an organization in the European Union that has been acredited by a member state to assess if a product meets certain preordained standards.

The five areas that are affected by the changes are audits and quality management systems, unannounced audits, major changes to technical documentation and technical file assessments, major changes for notified bodies, and changes to contractual arrangements between notified bodies and manufacturers.

The following points apply in relation to the new legislation:

- The manufacturer's premises and critical subcontractors and suppliers will need to be audited.
- Notified bodies will need to assess more critically whether the organizational structure and the qualification and competence of managers and staff are adequate to ensure compliance.
- Clinical evaluation of medical devices will remain a high priority, so manufacturers should expect their processes and their decisions and documented justifications to be challenged more often during audits.
- Manufacturers will be expected to use all available sources of postmarket surveillance data including distributors, users, and patients.
- Notified body audits should be annual.
- The quality manual and policies must demonstrate that the manufacturer actively retains responsibility for all the directive requirements and all the critical processes.

UNANNOUNCED AUDITS

Another change has to do with unannounced audits, which will be carried out in a random manner once every 3 years. Manufacturers will have no prior notice, and most audits will last 1 day and involve a team of two or more auditors. Because the main manufacturing site will normally be the location of the unannounced audit, this will in some instances be the location of the critical subcontractor and not the location of the manufacturer. Unannounced audits and the accompanying testing represent the major additional direct cost to the manufacturer of these European Commission changes.

MAJOR CHANGES TO TECHNICAL DOCUMENTATION AND TECHNICAL FILE ASSESSMENTS

Manufacturers must ensure that all technical documentation and certification can be "unequivocally" related to device types and to individual products via a product identification system.

MAJOR CHANGES FOR NOTIFIED BODIES

Notified bodies will be subject to much more scrutiny than before, including an audit team comprising three different competent authorities and the European Commission. Surveillance of notified bodies will now include annual assessments of their reviews of manufacturers' clinical evaluations. Additionally, notified bodies can be subject to unannounced audits.

CHANGES TO CONTRACTUAL ARRANGEMENTS BETWEEN NOTIFIED BODIES AND MANUFACTURERS

Agreed-upon periods of nonoperation will have to be defined when unannounced audits cannot take place. It will be the manufacturer's responsibility to inform the notified body of any change of dates. The absolute right to make unannounced audits to the sites of manufacturers or any predefined critical subcontractors will be included in contracts.

PRIORITY ACTIONS FOR MANUFACTURERS

Manufacturers should review their control of all critical subcontractors and suppliers. Manufacturers should ensure that they have effective systems for informing their notified body of changes to their processes. Manufacturers should ensure that there are written procedures describing processes that will ensure compliance with regulatory requirements. Manufacturers should ensure that all technical documentation has been updated in line with current device design and manufacturing practice. Best practice for manufacturers would be to immediately review the recommendation document and undertake an internal audit/gap review of processes and technical documentation to identify any areas of weakness and then to implement an improvement plan before the first notified body audit in 2014.

CONCLUSION

The documents described herein impose new requirements for notified bodies, more so than for manufactur-

ARE CHANGES TO THE CE MARKING PROCESS IMMINENT? (*CONTINUED*)

ers. The only requirement of manufacturers that have been following best practice is to institute procedures to manage unannounced audits. If manufacturers have fallen behind in terms of best practices, however, they will need to review and improve their processes in order to meet the new requirements.

Notified bodies are going to bear the brunt of the new legislation. Already, some notified bodies have dissolved, as they are not meeting the required standards. These changes are expected to take place early this year.

It therefore appears that the regulations will still be somewhat innovation friendly but may slow down the regulatory pathway in the process.

Arthur B. Cummings, MB ChB, FCS(SA), MMed(Ophth), FRCS(Edin), is a consultant ophthalmologist with the Wellington Eye Clinic in Dublin, Ireland. Dr. Cummings may be reached at abc@wellingtoneyeclinic.com.

1. Legislation. Official Journal of the European Union. September 23, 2013. http://eur-lex.europa.eu/JOHtml.do?uri=OJ:L:2013:253:SOM:EN:HTML

States during my training, I witnessed the difficulties involved in the process of transforming an idea into a real application and the huge costs involved. For these reasons, many clinical innovations have gone outside the United States for further development.

HOW IT WORKS IN EUROPE

In Europe, with a more reasonable medicolegal environment and an open approach to the application of new therapeutic techniques, innovations have been fostered, and investigators have played key roles in the development and application of many of them.

The advantages regarding innovation in Europe are clear: regulations foster new ideas, and people are more open to participating in advances. There are disadvantages in Europe as well, such as a lack of focus on vision research. I believe the concept of vision research needs an independent body to drive it in the European Union (EU), similar to the US National Eye Institute. Translational research suffers from a lack of active innovative laboratory research and a lack of an organized, well-funded, uniform policy for clinical research. Fragmentation in the EU and the lack of integrated research create a limitation for clinical trials, which counterbalances the advantages in some countries.

POSITIVE ENVIRONMENT

Despite these limitations, the EU offers a positive environment for clinical trials. Patients want to included in clinical trials, and they have a positive attitude toward medical research in general. One of the key factors in the present and future development of clinical research in Europe is the EVICR or European Vision Institute Clinical Research Network (www.EVICR.net). The EVICR.net, led by José Cunha-Vaz, MD, in Coimbra, Portugal, was created about a decade ago to bring together clinical centers in Europe interested and active in integrated clinical research. The goal is to create uniform standard operating procedures and certification in clinical research to qualify investigators, to certify processes related to the use of special technologies and therapies, to train researchers, and to assist in clinical investigations. This unique network is being reproduced in the United States.

As I am involved in the creation of the EVICR.net project, I have observed the evolution of the concept and its importance in global ophthalmic research. Studies are performed according to the expertise and the capabilities of each center, and various centers have different areas of specialization and focus. All of the participating centers are certified for clinical research and monitored by the general organization.

CONCLUSION

In general, Europe provides an opportunity for clinical research. Different countries may have different attitudes and laws, but an innovative company might find real opportunities to develop ideas into practice through the EVICR.net. More flexible and tolerant laws, although strict enough in terms of ethics and scientific merit, offer opportunities for clinical research in the EU. Europe will remain an area of preference for the development of innovations in the future, as the professional and scientific standards, strict adherence to the protocols, and patients' compliance are inherent in the European patients' culture and the doctors' education. ■

Jorge L. Alió, MD, PhD, FEBO, is a professor and the chairman of ophthalmology at the Miguel Hernandez University, Alicante, Spain, and the medical director of Vissum Corporación in Spain. Dr. Alió may be reached at +34 96 515 00 25; jlalio@vissum.com.