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CLINICAL LITERATURE REVIEWS: CHANGES IN THE EUROPEAN UNION'S MEDICAL DEVICE DIRECTIVE REQUIRE MANUFACTURERS TO TAKE IMMEDIATE STEPS TO COMPLY

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INTRODUCTION

With a rapidly approaching March 2010 deadline to comply with the European Union's revised Medical Device Directive, Nerac advises that manufacturers, now faced with an enormous amount of work to complete in a short period of time, take immediate steps to deal with the coming changes. At stake is maintaining or increasing share in the growing \$86 billion market that accounts for a significant percentage of most U.S. medical device companies' profits. With nearly 8,000 devices on the EU market, it is possible that a backlog of applications as the deadline approaches could bottleneck approvals, with serious implications for sales and profits. Applying Nerac's expertise in clinical research, companies can begin analyzing their product data now to make certain that they have initiated the required procedures to prevent disruptions to their sales pipelines.

Over the course of time, manufacturers often change to their products rendering the devices significantly different from the original designs for which a CE Mark was granted. The new directive, titled Directive 93/42/EEC of the European Parliament and of the Council, which still relies upon "Guidelines on Medical Devices—Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies," MedDev 2.7.1, alters the language to require manufacturers of any medical device sold in the EU to show proof of safety and efficacy before they can continue to sell the device in any of the 27 EU member nations after the March 2010 deadline. In addition to implantable devices, Directive 93/42/EEC has been significantly expanded to incorporate all Class II devices, thus affecting thousands of companies that may not have been required to submit any clinical data in order to sell their products in the EU. In fact, previously approved devices are now being carefully checked for continued compliance with their original approval. If even one significant change has been made, the device must go through the approval process again. If the clinical data is missing, Directive 93/42/EEC clearly states that the product must be withdrawn from the market until compliance is established. This approval process could easily take up to a year, perhaps longer as the deadline approaches.

CHANGES TO MEDICAL DEVICE DIRECTIVE

One of the most important changes deals with defining what clinical data can be used to demonstrate safety and performance. Clinical trial testing is one option, though it requires a lengthy, expensive process. An alternative is a clinical literature review of published data for similar devices. However, the new guidelines tighten the equivalence rules, requiring reviewers to establish an exact comparison. To meet the new requirements, medical device manufacturers are encouraged to employ outside parties to conduct independent evaluations to ensure compliance

with the new rules. Conducting the literature review is the first step to discovering whether an exact comparison can be made and supported or whether the company needs to engage in a clinical trial.

It is clear that under the new guidelines, it is going to be extremely difficult to achieve or maintain CE markings on products previously approved using the “substantial equivalence” test. It will no longer be sufficient to cite other, similar products’ clinical data to support their CE marking application. Clinical literature reviews will be required to cite nearly identical products. Many larger companies will therefore be performing clinical trials instead, which is not an option for smaller companies or those with extremely novel devices. After receiving certification, companies will be required to do extensive post-market surveillance as part of their vigilance system. Thus, clinical literature reviews are in reality just one part of a larger research effort many companies are now facing. Nerac has extensive experience in post-market analysis and can help companies go beyond merely recording any device failures by partnering with them to take an active role in gathering performance results.

These upcoming changes will blindside many companies, especially those not actively engaged in introducing new products in the next 18 months, as they may not be aware that the revisions to the Medical Device Directive apply to them as well. It is imperative that companies begin working with their Notified Body now to determine which products might be subject to the new guidelines, even those already available on the market within the EU.

DEVICE CLASSIFICATION

Another critical change is that the clinical evaluation requirement, previously limited to implantable devices, has been expanded to incorporate all Class II and Class III devices. Previously, only Class IIb devices needed clinical evaluation, but now Class IIa devices are also included. Class IIa devices are generally used for shorter periods of time than Class IIb and do not contain any active substances. Beginning in 2010, any medical device that comes in contact with the interior of a patient must prove safety and efficacy either through clinical trials or a clinical literature review, with no exceptions. Even devices previously approved for sale in Europe will be required to provide this documentation.

Device classification usually dictates how clinical evaluations should be conducted, with an increased emphasis on clinical trial investigations for implantable Class III devices. In some cases, a comprehensive literature review is sufficient to summarize clinical performance of the

device being reviewed or for devices demonstrated to be equivalent. In other cases, conducting clinical trials is the only option. Manufacturers, however, tend to use literature reviews as clinical evidence not only to demonstrate compliance, but also to justify the decision not to conduct a clinical trial. In some cases, a clinical trial would be considered unethical, as those not receiving the treatment as part of the control would have their health and safety jeopardized. Thus, compilation of multiple clinical trials into a meta-analysis clinical literature review of all patients receiving similar treatment is used as the ethical alternative. Nerac has experience with conducting meta-analyses, which clients can use as an alternative when they need more than a clinical literature review but cannot afford the time and expense of a clinical trial.

WHY CLINICAL LITERATURE REVIEWS

The question of choosing clinical literature review over clinical trial can be a daunting task in cases where preclinical or technical data are insufficient to demonstrate the absence of residual risk versus the benefits of the device. In such cases, a critical and unbiased evaluation of available literature by an outside party can determine whether to follow clinical trial route or the clinical literature review route. When Nerac analysts conduct literature reviews, they want to ensure that they are effective and that all requirements have been taken into account by answering these questions in advance and throughout the process:

- Are the results, conclusion and opinion confirmed and substantiated with data?
- Are the data and literature references in accordance with current regulations and state-of-the-art practices?
- Are the publications and data from reliable and credible sources?
- Are these publications peer-reviewed and did they follow all the procedures of a reliable scientific paper?

Clinical literature reviews constitute effective alternatives to time-consuming and costly clinical trials that entail recruiting expert investigators and vetting them for conflicts of interests, recruiting large numbers of volunteers, and investing long periods of time to record and evaluate the results. In some cases, it is infeasible to recruit enough volunteers to test a new medical device, making clinical trials impossible without including the results of a meta-analysis of the clinical literature. So even with the new rules, literature reviews present a more efficient path to approval.

A clinical literature review entails gathering and examining clinical data to assess risk, benefit, and performance of devices similar to the product under review. Only clinical data, which the European Commission guidelines define as information relevant to the various aspects of the clinical safety and performance of the device, can demonstrate that the device conforms to regulatory requirements.

The results of all the clinical investigations relevant to the device in question can help to identify risks. For some devices employing both the literature route and clinical trials are required. And if the clinical evaluation is based on such a combination, it should also include an overall assessment that takes into account all market experience, if available.

WHAT IS A CLINICAL LITERATURE REVIEW?

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ESTABLISHING EQUIVALENCY

When a literature review is being used as the primary source of information, the equivalence of the cited devices to the manufacturer's device must be clearly proven. The literature review must unequivocally demonstrate equivalence in design and performance in a specified application. The accuracy of this equivalence is a crucial factor and can determine if a clinical trial will be required instead.

Thus, a literature review should contain a description of the methods of weighting different papers and the statistical methods of analysis employed, taking into account the assessment methods, the type and duration of study and the heterogeneity of the population included within the study.

The conclusion of the literature review should include an analysis of the market experience of the same or similar devices, including the results of post-marketing studies, post-market surveillance and short- and long-term adverse events. This is in distinct contrast to the earlier Medical Device Directive, which had no significant post-market surveillance component.

The conclusion should also contain a list of publications, appropriately cross-referenced in the evaluation. If the clinical data proves substantial equivalence, the literature review should contain a statement that equivalence with all the relevant characteristics has been demonstrated and further include a justification, including an assessment of any probable benefit to health from the use of the device as intended by the manufacturer.

OBJECTIVITY IN LITERATURE REVIEWS

Some companies choose to prepare clinical literature reviews in house. This is risky. Notified Bodies are prone to rejecting in-house reviews because regulators understand that it might not be in the company's best interest to disclose negative findings. Clinical reviews are best undertaken by objective, qualified third parties, skilled in both the discipline of literature review and the interpretation of technical reports. Nerac has been providing clinical literature reviews for its clients for years, but now more than ever, this is a valuable service due to the changes in European requirements. Section 4.3 of the European Commission's MedDev 2.7.1 guidelines requires that literature reviews be performed by a party "suitably qualified in the relevant field, knowledgeable in the 'state of the art' and able to demonstrate objectivity." When selecting a third party for a literature review, the following criteria should be considered:

- The party's background and expertise in relation to the particular device or medical procedure involved.
- The party's knowledge of current medical practices for the device or procedure.
- The party's access to clinical literature databases both within the U.S. and abroad.
- The party's knowledge of and conformance to MedDev 2.7.1, which has a detailed format that must be followed.

Having the clinical literature review evaluation conducted by an unbiased, third party research organization like Nerac that has the necessary tools and qualifications for an effective clinical literature review can be a big step in avoiding many pitfalls and challenges in the process. Biases in representing adverse events data is more likely, especially in cases where clinical trial investigations are sponsored by companies with established physician relationships, many of whom are co-developing a device. Both EU and FDA reviewers will continue to be vigilant to accuracy and bias in data reporting, and this clearly demonstrates why many manufacturers intend to engage a third party's objective opinion in literature review.

CONCLUSIONS

As the looming 2010 deadline to comply with the requirements of the European Union's new Medical Device Directive approaches, manufacturers need to take an active role now in complying with the requirements for CE marking. Those companies, especially manufacturers of Class II devices, risk losing access to this \$86 billion market. With almost 8,000 devices sold in Europe, manufacturers can expect to be faced with considerable delays if they fail to take action now.

Companies need to begin analyzing their clinical data evaluations, making certain they are objective, unbiased and prove equivalence.

A key step toward establishing compliance is to retain a qualified, objective third party, such as Nerac, to determine if the less expensive literature review route is an option for some if not all of a companies' current and near future medical devices destined for sale with the EU. Companies also need to establish a post-market surveillance vigilance system. Between working with their Notified Body and a partner such as Nerac, companies can develop a plan to determine what steps will be necessary to ensure the continued success of each of their medical device products.

ABOUT THE AUTHORS



Deborah Schenberger, Ph.D.

Nerac Medical Device Analyst Deborah Schenberger, Ph.D., brings 16 years of industry and two years of academic experience and insight to medical device companies to help companies achieve product approval through the FDA, ISO, and CE registration processes. Dr. Schenberger has successfully submitted multiple medical devices to Notified Bodies for approval. She has also written numerous clinical literature reviews on behalf of clients, all of which have met with the approval of the clients' Notified Bodies. Before joining Nerac, Dr. Schenberger was a research scientist and teaching professor in bioengineering at University of the Pacific. As a graduate student at the University of California at Davis, where she earned her Ph.D., she studied micro-fabricated sensor development for spinal fusion applications and was a teaching assistant in the Human Anatomy Lab. As part of her dissertation, Dr. Schenberger designed and patented a biomedical sensor for measuring the onset of spinal fusion. Before returning to college, she was an engineering manager at Synvasive Technology, where she designed medical devices for the orthopedic industry. At Ortho Development Corp., she was a product development manager, designing orthopedic implants and instruments. She also spent several years designing mechanical systems with controls for NASA, and later for an entertainment robotics application. Dr. Schenberger was section chair for the American Society of Mechanical Engineers in 2007-2008, and is also a member of the American Society of Biological and Agricultural Engineers (ASABE), the Biomedical Engineering Society (BMES), and the Institute of Biological Engineering (IBE).



Marco Bafan

With a diverse academic and professional background and close to 10 years industry and research experience, Medical Device Analyst Marco Bafan partners with companies to develop innovative R&D solutions by conducting competitive reviews, assessing technology solutions, and examining market opportunities. Mr. Bafan's industry expertise includes both the business strategy and hands-on research of the commercial biomedical and medical devices industries. As a business development manager, at BioGenex Inc, a California biomedical company, Mr. Bafan helped to successfully launch new products and devices, working closely with sales and marketing teams to generate and grow business in designated territories. He was also responsible for negotiating contracts exceeding \$100,000 with major Pharma, hospitals and healthcare organizations. As a general operation manager at Lloyd's, an alternative medicine and nutrition company in Northern California, Mr. Bafan grew sales to more than \$1 million by developing new marketing tools and sales strategies. Mr. Bafan, who studied and researched biomechanics of heart valves at St. Jude Medical center, holds a master's degree in biomedical engineering from California Polytechnic University.

ABOUT NERAC

Nerac Inc. (www.nerac.com) is a global research and advisory firm for companies developing innovative products and technologies. Nerac analysts are uniquely qualified to conduct objective, third-party clinical literature reviews to assist companies in meeting the European Union's new medical device requirements. Nerac analysts also deliver custom assessments of product and technology development opportunities, competitor intelligence, intellectual property strategies, and compliance requirements through a proven blended approach to custom analysis: review of technical knowledge, investigation of intellectual property, and appraisal of business impacts. Nerac deploys analysts in diverse disciplines to help clients discover new applications, serving as a catalyst for new thinking and creative approaches to business problems or identifying strategic growth opportunities.

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