EuroIntervention

A user's guide to overcoming roadblocks: the European approval process

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Editors note: Susanne Ludgate has been involved with the management of clinical investigation systems for new medical devices in the UK and Europe as a member of the European Commission Working Party on clinical investigations of medical devices. Dr. Ludgate worked on the writing of the CEN and ISO Standards relating to these types of investigations.
The following remarks were made at the 2005 TVS symposium and forms an interesting counterpart to the previous article on the FDA.

As you can imagine, we do things differently in Europe. I think we have to look very carefully at why the Europeans come into this picture at all. I think there are two reasons: the first is that, after North America, Europe is the second largest purchaser of medical devices in the world. It is also the second most common place after North America to carry out clinical trials in the world. I think it is quite important that people know a bit about the European system, how it works and what the roadblocks are to gaining approval in Europe and how you overcome these. The first roadblock is knowing your system, how does it work and what are the differences. The basis to the European system is the CE marking; every device coming into the market must contain the CE marking. This means that the device in question complies with the relevant essential requirements covering areas of performance, safety and risk analysis. Unlike the North American system, the European system does not involve a central system for affixing the CE marks. This function has been devolved to what we call Notified Bodies. These are independent accreditation bodies that have been appointed by the Regulatory Agencies. There are about 80 of these across Europe. A manufacturer may go to any one of these that cover the device in question. What do these bodies do? Their functions include ensuring that the CE has been correctly applied, undertaking a quality systems audit, assessing technical files and the design dossier, where appropriate, and ensuring that there is a post-marketing monitoring system in place. The stringency of what they do is proportional to the risk of the device. The audit is repeated usually on a two to five year basis.

So how does a manufacturer decide what data is necessary to get the CE marking and approval from the Notified Body? First of all, you identify which of the essential requirements apply to "my" device and what information do I need to demonstrate compliance, eg bench testing, animal testing, clinical data. For the sort of devices that we have been talking about in the last two days, the very high risk, the new, novelty devices, there is an absolute need for clinical data. The Regulations state that there are two ways to obtain that clinical data. You can either go through the literature route and that consists of having data on your own device, maybe from trials that you have done elsewhere in the world or maybe from just the use of that device extensively somewhere else in the world. The literature route may be based on other people's data, in such that "my data" is just like another's and that other devices show data showing safety and performance which you could use since the devices are similar. If there is no clinical data from the literature, you will need to generate these from a specifically designed clinical trial. If you are going to go down the literature route, there are certain principles with which you will need to adhere. The first is that there must be adequacy of data. Anecdotal data is not sufficient. There must be enough data and scientifically rigorous to demonstrate that the devices is in compliance with the clinical essential requirements. If you are going down the route of being analogous to another medical device, you need to demonstrate equivalence across the board, and that covers a number of areas. You must show it clinically - treating the same type of patients in the same population. It must be equivalent technically, it must be a similar

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design or the same design with similar methods of deployment. It must also be biologically similar; in other words, you are using the same materials and the same underlying biochemical principles and characteristics.

If you need to mount a clinical investigation to generate your data, the law states that you must make an application to the Regulating Authority of the country or countries where you are carrying that out and they then have 60 days to say yes or no, we think this is okay to go ahead or we think it is unsafe. This period cannot be extended; we must give you an answer in that time. Some Member States have devolved that function to the Ethics Committees but, in the UK, we very firmly took the line that our Ethics Committees did not have the technical knowledge or the in-depth knowledge of medical devices in order to really assess whether things were safe or not. Therefore, we have our own assessment process with our own internal and external assessors. Finally, once you get to market, you must have in place some form of post-market monitoring system. There is nothing prescriptive in the Directive about it but obviously it is going to depend on the risk of the device, the novelty of the device, the type of the device. The types of devices we have been talking about have a very strict and controlled post-market surveillance system. It may include post-market clinical studies. For example, if you have a stent, you may have taken it to market on the basis of clinical data from 9 months to a year and you certainly want to extend that to find out the long term performance and side effects. It will always involve adverse incident reporting and you have to remember that, alongside adverse incident reporting, there is a requirement or clause in the Directives that states that the Regulator has the right, if there are concerns about public health and safety, to remove that device from the market, a so-called "safeguard" clause.

Roadblock No 1: know your system.

Roadblock No 2: know the differences between the American and European systems and the differences are really quite profound in terms of the data needed. First of all, if you are an American company, you must either have a presence in Europe or you must have an authorised representative. You must be aware that the endpoint in Europe is performance; it is not effectiveness or efficacy and that is going to make a difference in the data you are going to need to produce in support of your device and it is going to make a difference in terms of some of the clinical trials. You need to be aware that the standards underpinning the requirements of the law are sometimes quite different, particularly in the areas of quality systems and clinical data and evaluation. You also need to know that reimbursement will be quite different. It is different from country to country and in the UK it may be different from hospital to hospital.

Roadblock No 3 is the Regulator. I know you think they are there to say no to everything or maybe are there just to irritate and upset surgeons and manufacturers but, actually, we really do have a function. We have a function in terms of ensuring patient and user safety, ensuring that devices coming onto the market really are fit for purpose, and that devices going up for clinical trial have had all the necessary clinical and pre-clinical testing done and, actually, the next logical progression is to undertake a human trial. My advice in overcoming this roadblock is know your Regulator. It is important because there are a number of areas in which you are going to have to have direct contact and clinical investigation is one of them. When you are doing a clinical investigation, we all know the sort of data we are going to need. We need to know that there are safe manufacturing procedures. We need to know that you have done all of the preclinical testing, that you have identified the risks and the hazards and you have addressed these. But a lot of manufacturers and clinicians find it difficult to know what actual information is required to underpin and address these principles. What you need to do is come and talk to us and talk it through with us. We will also have direct contact with you in terms of adverse events, whether expected or unexpected. I was very unimpressed the other day to be informed by a manufacturer of a ventricular assist device, who had not told me about the deaths in his trial, that he did not need to because death was expected and you do not need to know about that. We do need to know and it does need to be reported to us. We will work through the investigations with you, if that is necessary, brining in the clinicians. We will bring details to collate, to establish trends, if necessary, and we will take action on the basis of that, because the last thing we want is action to take you off the market if that is not necessary. What we may do is work with you to try and overcome the identified risks and problems and, indeed, in the UK last year, we identified, in over 1,000 cases, changes that needed to be made to the manufacturing systems because of adverse events, without taking devices off the market. Lastly, we can help you in terms of humanitarian use. We will need to be in contact with you over that. It is when there is a real need, on a known patient basis, because there are no alternatives, and we can handle these very quickly for you, if there is a need. We will, of course, need information. We will need for you to fill in a form. We need to know the background, why, prognosis, what is going to happen to this patient if they do not get this device. We will also ask you to keep us informed; to let us know about any side effects. If you want any tips of how to handle the humanitarian use of a device, talk to the Regulator.

The Regulator, therefore, can help you. It is not just overlooking the patient and maintaining patient safety but I think we can help in innovation; we can help to move new developments forward, but we do need to do this with manufacturers and clinicians. We must understand where you are trying to get to; what you are trying to achieve and try and work within the regulations to do that. At the end of the day, that may have a knock-on effect in terms of minimising liability for you.

I hope this has given you a flavour as to what the European system is about. It is different in what it is trying to achieve; what the roadblocks are to achieving that. There are differences but these can be overcome by learning to know the system by identifying where the differences are and how you can address them in a way that works within the regulations. It is also very important to work with your Regulators here. I think the days of keeping people at arms' length are long gone, it is not feasible anymore. We need to talk to you upfront for advice; we need to offer you meetings and video and teleconferences. Actually, at the end of the day, what we really want is to help you get through the system, to take a CE marked device to market, to keep that CE marking and also to make devices that are going to make a difference to patients clinically available to all surgeons in a safe way.