Regulatory issues for on-line haemodiafiltration

Dario Pirovano
Consulting Director, Medical Technology Consultants, Belgium

Key words: medical device; medical device directive; on-line haemodiafiltration; regulation

Introduction


The Directive, published in 1993, was introduced on a voluntary basis at the beginning of 1995, and it is due to become mandatory on June 14, 1998. According to the rules of the European Union, all 15 Member States should have published national laws implementing the Directive by July 1994. To date, 14 Member States have published such laws (the only exception being Belgium) which also contain provision for the withdrawal of pre-existing national legislation which remains applicable, alternatively, only up to June 14, 1998.

The major features of the Directive can be summarized as follows:

- Devices are defined as: ‘any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
  - diagnosis, prevention, monitoring, treatment or alleviation of a disease,
  - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
  - investigation, replacement or modification of the anatomy or of a physiological process,
  - control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means’

As appears clear from the definition above, there is no doubt that the machine used for on-line haemodiafiltration (HDF) is a medical device; however, there have been lengthy discussions on whether the concentrates used in on-line HDF or in other dialysis procedures have to be considered as medical devices or drugs.

The current view of the European Commission, as well as of the Member State Authorities and of the official testing institutions (the so-called Notified Bodies), is that concentrates fall under the scope of Community Directive 93/42/EEC on Medical Devices.

Devices are divided into four classes (I, IIa, IIb and III), depending on their intended use and on the hazards that the intended use generates. It is important to underline that, since the intended use of the device is totally at the discretion of the manufacturer, which, as we will discuss later, is the sole agent responsible for assigning to its products the performance limits it feels appropriate, the classification of medical devices is also determined by the manufacturers and not by an Agency.

Each and every class has its proper set of conformity assessment procedures which, while maintaining the manufacturer as the sole agent responsible for conforming to the directive, requires an additional intervention by appropriate testing institutions (the so-called Notified Bodies) proportional to the classification of the device (i.e. no control for Class I, total control for Class III). The manufacturer has, within the conformity assessment procedures for a given class, the choice between two or three procedures in order to fit the reality of its organization.

It is worth underlining at this point that, within the conformity assessment procedures of a given class, all procedures are equivalent and, with the permission of Mr Orwell, there is no procedure which is ‘more equivalent’ than the others.

When the manufacturer has fulfilled the applicable requirements of Community Directive 93/42/EEC on Medical Devices, it is entitled to affix on its products the CE marking, which assures the consumer that the device conforms to the directive.

The principal issue relating to the application of this directive, as opposed to previous regulatory requirements, is that the CE marking does not indicate that the product has to be considered generally ‘safe’, since it complies with a standard which could be more or less appropriate for the product, but it indicates that the product is safe exclusively when used as indicated by its manufacturer in the accompanying documenta-
tion, in combination with other devices as indicated by the manufacturer in the accompanying documentation and within the limits of performance indicated by the manufacturer in the accompanying documentation.

The user of medical devices must therefore pay the utmost attention to the content of the accompanying documentation (labels and instructions for use) which is the only valid document to determine whether a given device is suitable for the specific treatment he intends to deliver to a patient. Consequently, in the event that he reads that the device is not intended to be used in a certain way, under certain circumstances or with other specific devices, he must refrain for using it for that treatment or, indeed, not buy it.

To use an example, if a manufacturer claims that its electromedical device can be operated safely with a supply voltage between 210 and 230 V and the hospital buyer knows that its electrical supply may have fluctuations outside that range, he should refrain from buying the device or introduce appropriate measures for maintaining the voltage fluctuation within the limits specified by the manufacturer.

The user must at all times bear in mind that the CE marking ensures safety only when the device is used as intended by its manufacturer and as indicated in the accompanying documentation; any other ‘intended use’ suggested verbally by the manufacturer or its sales force has not been the subject of appropriate evaluation from the safety standpoint, therefore the device used outside the specification given by its manufacturer in the accompanying documents does not bear the CE marking legally.

Another important meaning of the CE marking is that the manufacturer ensures, by affixing it to the product, that the performance claimed for that product can be attained.

It is worth, here, enlarging on this concept of performance which has been one of the most contentious issues during the development and negotiation of the Directive.

Previous legislation, as well as the Medicinal Products legislation and the present American Food and Drug Administration regulation were/are basing the evaluation of a product on its efficacy, meaning by this the ability of the product to treat certain diseases, handicaps or injury.

The evaluation of efficacy is often made on the assumption that, if alternative methods are available and the new device does not show, in the reviewer’s opinion, a substantial improvement, the device does not have sufficient efficacy to justify its presence on the market. Since this kind of judgment is highly subjective, the time necessary for reviewing a device becomes quite long, and final approval is far from certain.

In the opinion of the European Commission and the EU Member States, this is not exactly the correct way of operating a regulation in a sector which is continuously and rapidly evolving.

In the opinion of the European legislator, the doctor is the only one responsible to decide whether or not a device, having a certain declared performance, is suitable for performing a specific therapy or diagnosis on a specific patient: if a device, in spite of its ‘limited’ declared performances, is able to save even only one life, it must be available to doctors.

**Particular remarks applicable to on-line HDF**

For the sake of this part of the article, we will assume that on-line HDF is a combination of an electromedical device, of some disposables and of the concentrates.

From what has been said above, the three components should have been indicated by their manufacturers as being appropriate for use with each other, either by an explicit reference, or by referring to the characteristics necessary for the correct use of the different devices.

While the application of Community Directive 93/42/EEC on Medical Devices to the ‘machine’ part of the system and to the disposable part of the system does not pose particular problems as compared with any other medical device, the concentrates do need some clarification.

Making an analogy with the example of the electromedical device rated for 210–230 V mentioned above, the concentrates for on-line HDF should be supplied with the exact indication on the quality of the water which must be used. In doing so, the manufacturer assumes the responsibility of ensuring under what circumstances the concentrate and, consequently, the entire system are safe and perform as specified. Any difference in the characteristics of the water results in the use of the device in a manner which has not been subject to appropriate verification. In other words, the combination of the various devices and, in particular, the concentrates, when used with a water which does not have the characteristics indicated by the manufacturer, becomes a ‘new’ device since the intended use is changed; consequently, in order to bear the CE marking of conformity to Community Directive 93/42/EEC on Medical Devices, it should be subject to a new conformity assessment procedure.

Continuing this analogy, this means that the concentrates should be used by a given user only when, for example, the user is capable of exerting an appropriate and continuous control of the characteristics of the water, used to dilute the concentrates, which have to be maintained within the limits specified by the manufacturer of the medical device. In order to exert such control of the water, the user should have a structure, appropriately organized, which allows him to take full responsibility for this issue. If the user fails to be able to do so, he should choose other HDF systems rather than risk using the device outside its specifications, since this would put the entire responsibility for any accident on his shoulders.

Let us now briefly discuss an aspect related to the use of on-line HDF as opposed to traditional HDF which shows quite explicitly the differences between the traditional regulation and the new one. As is
known, the basic difference lies in the fact that, as previously mentioned, according to the present interpretation of the Medical Devices Directive, the concentrates used in on-line HDF are considered as medical devices, whereas the solutions used with traditional HDF are considered as medicinal products and are covered by a Pharmacopoeia Monograph. This latter circumstance, in spite of the well known saying that ‘something which is regulated by the pharmaceutical law is safer than a medical device’, might lead to potentially greater problems than those with on-line HDF. In fact, the limits given by the Pharmacopoeia, which were stated many years ago, do not consider the developments in the HDF technique which nowadays requires > 10 l of liquid to be administered to the patient. As a result of this, a solution which conforms perfectly to the upper limit for endotoxins given in the Pharmacopoeia might result in total delivery of endotoxins to the patient of 10 times more than the maximum bearable. It is only thanks to the self-discipline of the manufacturers of these products, who stay well under the limits imposed by the Pharmacopoeia, that this circumstance does not arise.

On the other hand, the manufacturer of the device ‘concentrate’ must, in order to be able to affix the CE marking, demonstrate under its full responsibility (and under the control of an official testing body, the so-called Notified Bodies) that the device is able to fulfil, for example, Essential Requirement no. 1 of Annex I of the Medical Devices Directive which reads: ‘devices must be designed and manufactured in such a way that, when used under the conditions and for the purpose intended, they will not compromise the clinical condition or the safety of patients … provided that any risk associated to their use constitutes acceptable risks when weighted against the benefits to the patient and are compatible with a high level of protection of health and safety’.

Help is given to the manufacturers, within the directive, by the obligation to perform a so-called risk analysis. For this risk analysis, which is compulsory for devices of all classes, the manufacturer is guided through the characteristics of its device in an organized manner, thus identifying all hazards related to the use of its device and analysing the appropriate methods to reduce the related risks.

In other words, this means that, in spite of any indication given in any Standard or in a Pharmacopoeia Monograph, the manufacturer has to take all necessary steps to ensure that its product is safe for the intended use and, consequently, assume all responsibilities in this sense without ‘hiding’ himself behind the blind conformity to such Standards or Pharmacopoeia Monographs.

Reference