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Regulatory Challenges of On-Line Hemodiafiltration

D. Pirovano

Pirovano Management SPRL, Brussels, Belgium

Abstract

The launch of on-line hemodiafiltration happened at a very peculiar time from the regulatory standpoint. The directives on medical devices were at their very beginning and the medicinal products regulatory regime was considering, after 30 years of operation of Directive 65/65/EEC, whether it was the case to go for greater harmonization. The success in the introduction of the therapy was strictly linked to the possibility of having the entire system approved for the European market according a single procedure. I had the pleasure to be part of the team, which included Dr. Wolfgang Kümmerle and my old friend Dr. Emanuele Gatti, which succeeded in gathering consensus on the classification of the on-line hemodiafiltration system as a medical device.

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Setting the Scene

I had the opportunity to work as a consultant for Fresenius some years ago on the regulatory regime applicable to the new concept of dialysis, developed by Fresenius, known as on-line hemodiafiltration.

The first challenge was to understand the product and its components. The new concept was intended to combine hemodialysis and hemofiltration.

The regulatory problem was mainly whether all the components of the on-line hemodiafiltration machine could or could not fall within the scope of the Medical Devices Directives which were at that time entering the regulatory scenario in Europe.

The major point of uncertainty was linked to the 'revolutionary' production of the electrolyte and of the dialysis solution by the machine itself, not using

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pre-produced solutions as was the case with the traditional hemodialysis and which were considered as drugs.

The advantage of having all components under the same regulatory regime was evident: the requirements for placing on the market a medical device and a drug are different under almost all aspects, starting from the applicable quality system, to the role of clinical investigations and, not least, the authorities responsible for the evaluation.

In particular at the beginning of the 1990s, the medicinal products regulatory regime was not fully harmonized in spite of the existence of a Community directive since 1965 (Directive 65/65/EEC). The system envisaged national authorizations for drugs, which could then be expanded to other countries through the so-called mutual recognition process. This process was neither easy nor quick and too many national deviations rendered it cumbersome and particularly uncertain and expensive. In those days the Commission was starting to consider the creation of a central agency for the approvals of drugs which saw the light only in 1995 (the European Agency for the Evaluation of Medicinal Products, now called European Medicines Agency), but which had a very limited field of operation.

On the basis of the above and in consideration of the work that the Commission was starting on a harmonized regulatory scheme for medical devices (see below), it was evident that the success of the introduction of hemodiafiltration was heavily dependent on the acceptance from the authorities that all components were classified as medical devices.

The History

At the beginning of the 1990s the European Union was finalizing two directives[1] aiming at harmonizing the placing on the market and the putting into service of a set of products used in healthcare which, from then on, were called 'medical devices' also in Europe[2].

The scope of this initiative was twofold: on one side to harmonize the regulatory requirements which were blossoming among the 12 member states which constituted at that time the 'Communauté Européenne', and on the other to clearly set the boundaries between the Medicinal Products legislation and the Medical Devices legislation.

We were in fact at the eve of one of the most phenomenal industrial developments in a single sector: the medical devices world was finding its way as an

[1] Directive 90/385/EEC on Active Implantable Medical Devices and Directive 93/42/EEC on Medical Devices.

[2] 'Medical device' was already a recognized term in the United States since at least 1976 and in the UK, but across the European Community these products were called several different names, some of which quite fancy (the best: *presidi medico chirurgici* in Italy).

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alternative or a complement to the well-established Medicinal Product sector and it was clear to the pioneers that the only way to avoid this sector being 'killed in the cradle' was to favor the European market access of these products with a single system, applicable only once and valid throughout the entire Community and to tailor it to its nature (scientific, technological and from the use standpoint) which is profoundly different from the one of the medicinal products.

It was never the intention to criticize the Medicinal Product regulatory system which was in place in Europe since 1965, but rather highlight that such a system was not, in spite of its stringency, going to ensure safe and effective devices on the market since, for example it did not consider the impact of the skills of the doctors using them, which could count up to 90% of the efficacy of the treatment.

Another concept which was marking the difference between devices and drugs was the iterative nature of innovation which characterizes the device sector as opposed to the drug sector. An implantable pacemaker, in its first shape in the late 1950s, was an ugly box, the size of a pack of cigarettes, weighing 64 g and needed to be recharged every week. The latest versions have the size of two 2-euro coins, weigh a few grams, can be implanted in day hospitals, and last several years. The most recent pacemakers use still the same basic concept of the first ones, but have developed technologically, while in the medicinal products area an innovation is generally considered a molecule which has a new unprecedented target receptor. The need to confirm safety and performance or efficacy of the two products is clear, but the methods to verify them cannot be the same because of their very nature.

This concept was hard to transmit (and apparently it is not easy now either). A number of authorities at that time were reluctant to expand the definition of medical device too much. Their intention was to keep many products under the medicinal products regime which was as said before largely of each member state's pertinence.

The new system was based on the so-called 'new approach'. This legislative technique aimed at setting the fundamental principles to be followed in order to guarantee safety and performance of a product, instead of fixing technical requirements which were difficult to agree on at political level. This was particularly true for the medical devices sector where there are some 400,000 'things' which fall under the definition and are designed and produced by a variety of different types of manufacturers (chemical, mechanical, electrical, electronic, etc.).

Another fundamental characteristic of the new approach was the separation of the duties and responsibilities in the pre- and post-marketing phase. While the evaluation pre-market should have been carried by independent third parties (notified by the National Authorities), the overall surveillance of the market was of pertinence of the various National Competent Authorities.

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Finally, it was apparent that not all the 400,000 'things' being medical devices needed the same degree of pre-market third-party evaluation: where the inherent risks related to the use of a tongue depressor could well be minimized under the sole responsibility of the manufacturer, the risk minimization related to the use of a heart valve needed to be verified by a third party before allowing the manufacturer to introduce the device on the market. A risk-based system was then put in place to classify medical devices into 4 classes with a gradual increase of the role of the third-party evaluation depending on the human vulnerability in case of failure of the device.

Those days, I had the honor to be chosen as technical expert within the Directorate General III of the European Commission to advise the Commission services on the technical issues pertinent to devices and I contributed to the drafting and negotiation of the directives.

The challenge was extremely fascinating for me who had been among the very first engineers to graduate from the Politecnico of Milan who were introduced to healthcare engineering. One of the other pioneers of this group of young 'bioengineers' was a certain Emanuele Gatti, with whom I had the chance and the pleasure to work with on different occasions for the last 30 years.

When the contract with the Commission expired and I started my career as a consultant, I was approached by Dr. Gatti who explained to me the challenges that Fresenius was facing in the acceptance from the authorities of the fact that all the components of the on-line hemodiafiltration system had to be considered as a medical device.

I then started working with Dr. Gatti and Dr. Wolfgang Kümmerle, who will surely contribute more technical details than me in another chapter of this book, and together we studied an appropriate rationale for the justification of the classification of on-line hemodiafiltration as a device.

We were lucky enough to find receptive ears among the Member States' experts which were sitting in the Classification and Borderline Working Group of the Commission and good enough to produce a solid rationale which supported the classification of the most 'critical' component of hemodiafiltration as a device on the basis of the letter and the spirit of the newborn directive.

The introduction of on-line hemodiafiltration in the treatment of patients then became a reality.

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Dr. Dario Pirovano is a consultant for regulatory affairs with Eucomed, the European Medical Technology Industry Federation since 2002. He worked in the European Commission for 4 years, where he contributed to the drafting and negotiating of the 90/385/EEC and 93/42/EEC Directives. He has over 30 years of experience in medical technology as designer and regulatory affairs expert. In 1995 he

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founded Pirovano Management SPRL, a consulting firm advising manufacturers, Notified Bodies and authorities in regulatory matters relating to medical technology. Dario can be considered the historical memory of the development of medical devices regulation in Europe. He holds a Doctorate in Engineering from the Politecnico di Milano.

D. Pirovano
Pirovano Management SPRL
Avenue de Messidor 306/16, BE–1180 Ukkel (Belgium)
E-Mail Dario.Pirovano@eucomed.org

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