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Facing Regulatory Challenges of On-Line Hemodiafiltration

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Abstract

On-line hemodiafiltration (on-line HDF) is the result of a vision that triggered multifarious changes in very different areas. Driven by the idea to offer better medical treatment for renal patients, technological innovations were developed and established that also constituted new challenges in the field of regulatory affairs. The existing regulations predominantly addressed the quality and safety of those products needed to perform dialysis treatment which were supplied by industrial manufacturers. However, the complexity of treatment system required for the provision of on-line fluids demanded a holistic approach encompassing all components involved. Hence, focus was placed not only on single products, but much more on their interfacing, and the clinical infrastructure, in particular, had to undergo substantial changes. The overall understanding of the interaction between such factors, quite different in their nature, was crucial to overcome the arising regulatory obstacles. This essay describes the evolution of the on-line HDF procedure from the regulatory point of view. A simplified diagram demonstrates the path taken from the former regulatory understanding to the realization of necessary changes. That achievement was only possible through 'management of preview' and consequent promotion of technical and medical innovations as well as regulatory re-evaluations.

Point of Departure

Millions of very efficient and safe applications have demonstrated for many years that the on-line hemodiafiltration (on-line HDF) treatment plays a dominant role in dialysis. This place of value rests measurable advantages for patients suffering from end-stage renal disease. The clinical benefits are attributed to the combination of the physical modes of action of hemodialysis (diffusion) and hemofiltration (convection). By combining the two therapy methods, both

the small and the middle-sized molecules can be efficiently removed from the patients' blood.

This specific way of treatment, called hemodiafiltration, is particularly beneficial if large volumes of hemofiltration (HF) solution are available as substitution fluids. Before the availability of the on-line procedure, HDF was performed using single-dose HF solution bags. These substitution bags were produced by pharmaceutical companies, filled into large volume plastic containers with capacities of up to 5 liters, sterilized, stored and transported to the dialysis clinics before being eventually applied by the clinical professionals. Due to complex logistic procedures, unfavorable handling and considerable costs, the provision of larger amounts of HF solution bags was limited. Consequently, the development of the on-line procedure was based upon the idea to prepare the dialysis liquids in situ during the treatment, thereby replacing many of the former logistic steps.

In addition to the technological challenges of on-line production of dialysis fluid, this new concept had to overcome high regulatory hurdles – the industrially manufactured single-dose bags are internationally classified as pharmaceuticals. For this reason, health authorities demand conformance with high quality and safety requirements before granting marketing authorization for finished products. Specific quality criteria primarily relate to the chemical purity and the microbiological safety of the ready-for-use solution (fig. 1).

Historically, solutions for parenteral application were manufactured in hospitals under the responsibility of pharmacists. The produced batches were only allowed to be administered to the patients by physicians after final control and release by these pharmacists in their authorized function. On-line prepared solutions, however, manufactured in the course of the treatment and infused into the patient without interim storage, final quality control and batch release were virgin soil, particularly regarding the regulatory assessment.

In any case, the one-line generated products must at least possess the same quality and safety characteristics as those solutions provided by industry.

An initial regulatory analysis of the major components necessary for preparation of on-line dialysis solutions revealed that a combination of medical devices and pharmaceuticals is required (fig. 2, components 1). As a particular difficulty, so-called 'borderline products' were part of the set of obligatory components.

These 'borderline products' had to be assessed and treated with special focus as they were classified differently by the national health authorities of the member states of the European Union (e.g. handled as pharmaceuticals in Germany but as medical devices in the United Kingdom). Dialysis concentrates were 'borderline products' of particular concern because these are essential raw materials for the production of on-line fluids. Shortly before the dialysis treatment, the concentrates are diluted with water of specified quality by electromedical equipment (the dialysis machine) and thus brought to the individual concentration required for the patient. In hemodialysis, dialysis concentrates are used as raw materials for the preparation of a dialysis solution that flows outside of the

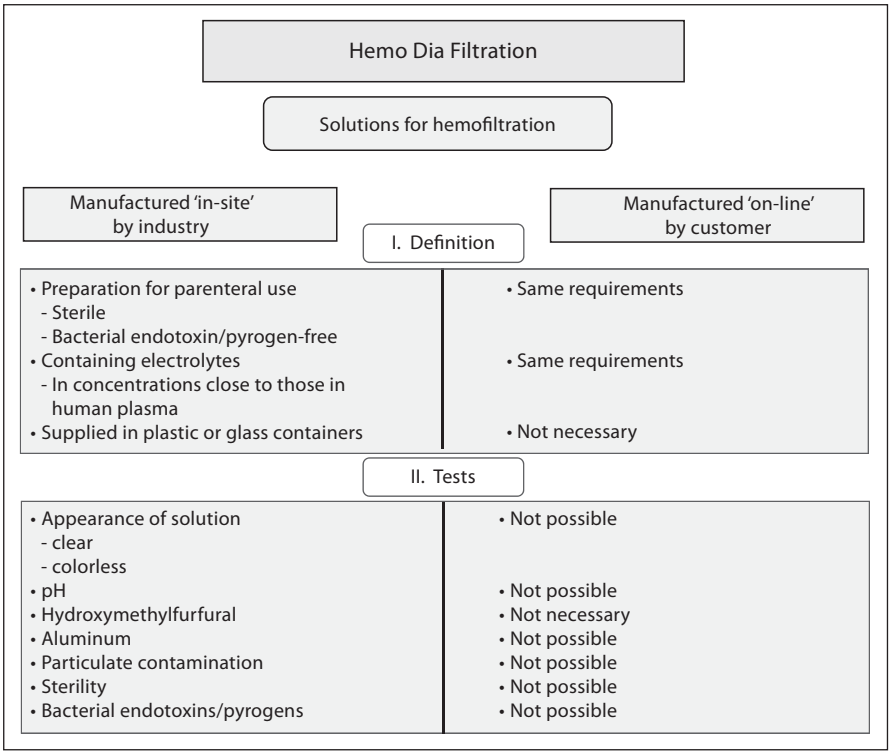

Fig. 1. Quality requirements for HF solutions.

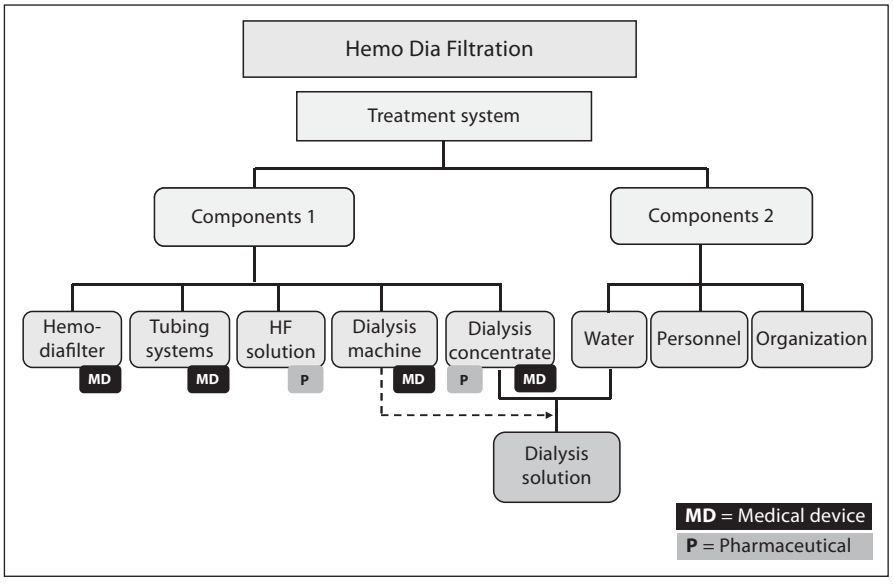

Fig. 2. Essential components for HDF treatment realization.

dialyzer membrane in a direction countercurrent to the blood flow. During this procedure, undesired, toxic metabolites are removed from the blood by means of purely diffusive action.

The on-line HDF procedure uses the same raw materials and applies the same manufacturing method for the preparation of the solutions. However, the resulting fluid not only passes along the outside of the dialyzer's membrane but it is simultaneously infused into the blood circuit of the patient. This new concept of producing dialysis solutions also for the purpose of direct infusion raised new regulatory challenges.

The main tasks to be solved were the provision of the following evidence: (a) evidence that the raw materials used for the preparation of on-line hemodiafiltration solutions possess the required quality; (b) evidence that the manufacturing procedure for on-line dialysis solutions generates products of the required quality; (c) evidence that the infrastructure in the dialysis clinics ensures the required features (see fig. 1, components 2), and (d) evidence that health authorities and notified bodies grant necessary regulatory approvals for all components concerned.

Evolution of the Regulatory Environment

Realization of the various challenges required a circumspect management, both overseeing the whole chain of necessary components and understanding the mutual dependencies and potential risks triggered by the innovative concept. The barriers then in place threatened to prevent the new system from duly gaining market access. In particular, marketing authorizations of certain essential components required by the on-line system were missing. It was Dr. Emanuele Gatti who first addressed the coherence of the medical expectations, the innovative technology and the arising regulatory barriers by a holistic approach. Fresenius Medical Care (FME) employees and external experts were subsequently brought together to identify the basic regulatory obstacles and propose possible solutions. In particular, this FME initiative was supported since 1994 by Dario Pirovano, a technical expert with profound knowledge and experience in European legislation and co-developer of the draft of the new medical device directives. The common project started with the regulatory analysis of the existing directives, laws and standards regarding their scope and applicability to on-line procedures [1, 2]. The primary target was to have existing regulations either reworked or, if necessary, to have suitable new standards elaborated that considered the state of innovation and the expectations of the different stakeholders.

At that time, the European regulatory bodies were about to review the different national requirements aiming at harmonization and classification of medical devices and pharmaceuticals. During this period, borderline issues were

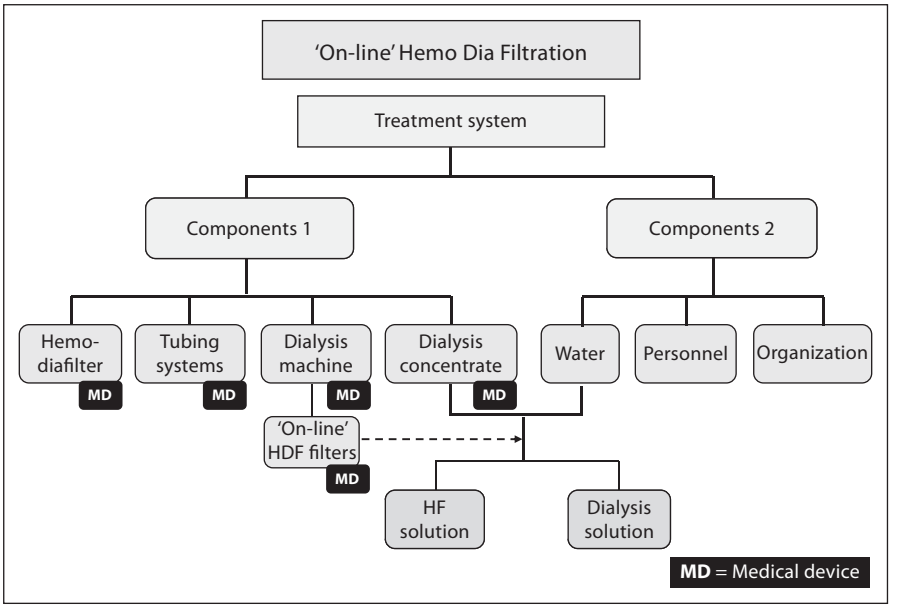

Fig. 3. Essential components for on-line HDF treatment realization.

discussed and assessed by many different parties in order to arrive at a common European understanding. Utmost attention had to be paid to the principal action that the product is intended to perform in or on the patient. After intensive and often controversial discussions of the working group established by the European commission on drug/device borderline issues, the hemodialysis concentrates were allocated to the medical device regulations all over Europe [3]. The explanatory statement concluded that hemodialysis concentrates are medical devices in their own rights as they are '. . .materials . . . used in combination with other medical devices, . . .intended by manufacturers to be used for human beings for the purpose of . . . treating a disease . . . and which do not achieve their principal intended action by pharmacological, immunological or metabolic means' [4]. With this final decision, the pharmaceutical status of concentrates was overcome and all components necessary for the generation of on-line fluids were defined as medical devices in all member states of the European Union and, later on, also beyond the EU borders.

Following this accomplishment, the same regulatory regime could be applied for all components needed for the preparation of on-line in a significant number of target markets. As a consequence, the pharmaceutical regulations had to be replaced by medical device standards and the responsibility switched from the Pharmacopoeia commission bodies to the CEN/CENELEC groups. Without delay, the requirements for the quality of dialysis concentrates were set by a new ISO

standard. This norm focused on the hemodialysis procedure and covered 'related therapies', a category that also included innovative on-line procedures [5].

The new international standard mirrors the evolution of European harmonization by stating in the introduction: 'The term consensus . . . does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests must be merged'. Nevertheless, by the generation of this standard, conscientious efforts of many parties such as physicians, clinical engineers, nurses, dialysis technicians, device manufacturers, notified bodies and governmental representatives succeeded in overcoming regulatory roadblocks for the sake of innovation and, eventually, for the better treatment of dialysis patients.

In the following period, additional ISO standards were established or updated which specified the quality of the water for dialysis and of ready-for-use dialysis fluids [6, 7]. Later, the water preparation equipment was also classified as a medical device in Europe, and the corresponding requirements were specified [8]. FME employees with special expertise steered or participated in the relevant standardization working parties and introduced requirements for on-line HDF treatment. Particular focus was placed on the dialysis machine. This constitutes an essential part of the treatment system because this electromedical device quasi serves as production equipment of the on-line dialysis solution. The development of innovative components and new control mechanisms facilitated the efficient purification of the microbiologically burdened input solution. Double filtration through polysulfone membranes ensured that the resulting output is a sterile, endotoxin-free on-line prepared fluid. Performance, safety and functionality of the on-line HDF equipment were verified by an independent test house. Type testing according to international standards was successfully passed and eventually the CE certification as medical device was granted.

Finally, after all raw materials and system components had gone through the European medical device conformity assessment procedures, all necessary parts for on-line HDF were available for clinical use at full regulatory compliance. Moreover, FME ensured the correct and safe application of the whole treatment system by the definition of rules, procedures and guidelines which were summarized in a dedicated quality management system. FME decided to implement this newly developed clinical quality management system in its company-owned dialysis centers, particularly focusing on the quality and safety of on-line produced fluids. Appropriateness and efficacy of the necessary organization and specified procedures are regularly audited in the FME dialysis centers and assessed by external experts according to internationally recognized standards. The high quality of FME products, clinical infrastructure, medical performance and notably the smooth interplay of all components is virtually demonstrated by the certification according to ISO 9001 standard and Good Dialysis Practice rules.

This integral approach reflects the conviction of the responsible management of FME: quality and safety can be ensured at best if products, personnel and an

appropriate infrastructure work together and are continuously improved in a systematic manner by a committed management and motivated personnel.

Conclusion

FME successfully managed the introduction of a complex, multifactorial treatment system which set new standards in dialysis. The innovative approach also triggered changes in the respective regulatory environment in Europe and beyond.

The combined understanding for medical improvement, technological innovation, regulatory evolution, new quality standards and organizational arrangements ensured the realization of a safe and effective therapy system which has been verified to be state-of-the-art in modern dialysis treatment.

It was Dr. Emanuele Gatti who recognized, right from the beginning, the importance of regulatory compliance. He took the lead and oversaw the different aspects involved in the realization of the concept. Besides the identification and motivation of appropriate people for the arising tasks, he brought together diverse disciplines and cultures. This approach resulted in an innovative dialysis therapy system performing safe treatments of high quality which are based upon a new and consistent regulatory regime.

The retrospective assessment of this regulatory evolution concludes an important step from the view of the quality and safety of a single product up to the consideration of the performance of a whole treatment system – a step that is crucial for the meaningful understanding of such a complex therapy system as presented by on-line HDF treatment.

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