ORIGINAL ARTICLE

Regulatory measures for implementing new medical devices. Recalling Boneloc®

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ABSTRACT

Through the past decades, new medical devices have been introduced at an increasing pace at the urge primarily of manufacturers, clinicians, and patients. Whereas it is mandatory to assess and approve new pharmaceuticals before their widespread use is allowed, innovations in medical devices generally have not been subject to the same restrictions. The European Communitys program on completion of the Internal Market has generated a series of three Directives regulating the safety, reliability, and marketing of practically all non-pharmaceutical medical products. Once CE-marked, devices are available throughout the Union, an area constituted of nearly half a billion citizens after the expansion to 25 Member States.

Before the European Union Directives were implemented, Boneloc® was introduced to commercial distribution in the beginning of the nineties as a new and promising bone cement to be utilized in joint arthroplasty prostheses. While promptly gaining wide acceptance in most of the Nordic countries, Boneloc® was after few years and about 5,500 implanted Scandinavian patients withdrawn from the market abruptly because of inferior fixation properties.

Utilizing Boneloc® as a test case, the present study critically examined whether a comparable incident could occur after the implementation of the European Union Directives and what strategies can be applied to avoid equivalent future misconduct.

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Over the past four to five decades, advances in medical device technologies have contributed substantially to alleviating patients' pain and suffering as well as improving their functional status and well-being (1). The incentive of manufacturers, clinicians, and patients for acquiring new and conceivably improved medical technology is strong and new devices are being introduced at an increasing pace. While it is mandatory to assess and approve new pharmaceuticals before their widespread use is allowed, innovative medical device technology generally has not been subject to the same restriction. However, with the establishment of the Single Market, the European Economic Community (EEC) has since the nineties issued a series of three directives to ensure product safety and reliability of all medical devices. The last of these directives became active within the Member States on December 7, 2003.

In the United States, since the beginning of the nineties there has been a substantial interest in the approval process of medical devices particularly in certain areas such as breast implants (2, 3). In the Scandinavian countries, the attention has recently focused on orthopedic implants also. Along with numerous prosthetic designs, different types of bone cement have been introduced in order to increase prostheses' survival in joint replacement surgery (4, 5). The shortcomings of conventional cement include bone injuries secondary to heat generated during the polymerization process and leakage of toxic chemical compounds (6-12). Additionally, the peroperative leakage of volatile monomers represents substantial health problems for the nurses and medical staff engaged in these arthroplasty operations (13, 14).

The Boneloc® cement was developed in Denmark and introduced to commercial distribution before the European Union Directives were implemented. The proposed merits of Boneloc® were to reduce the injurious biological effects occurring during and after cementation of joint implants as well as minimizing operation room personnel to exposure from toxic vapors while at the same time maintaining the mechanical properties of the cement (15). The integrated mixing and delivery system was an innovation awaited since the introduction of bone cement with toxic volatile monomers. Shortly after being placed on the market, Boneloc® quickly gained wide acceptance in most Nordic countries, and approximately 5500 Scandinavian patients receiving total joint replacements were implanted with this type of cement. Yet, approximately four years after the introductory marketing in 1991, Boneloc® was withdrawn from distribution abruptly because of inferior fixation properties.

Utilizing Boneloc® as a test case, the present study analyzed whether an equivalent incident could occur after implementation of the European Union Directives and what strategies can be employed to avoid similar future reoccurrence. The past and existing regulatory measures in the Nordic countries and the European Community's program for introducing new medical technology were scrutinized.

LEGISLATION

CLINICAL RESEARCH

Since long medical ethics constituted an important area within the dimension of human research in the Nordic Countries. Approximately ten years after the introduction of the First Declaration of Helsinki, the Nordic Medical Associations decided to revise it. Three Scandinavian designees were endorsed to amend this Declaration (16, 17), and the Second Declaration of Helsinki was adopted by the Nordic Medical Associations as well as the 29th World Medical Assembly in Tokyo, Japan, October 1975. Later the Second Declaration of Helsinki has been amended on several occasions (18).

The Nuremberg Code, the Declaration of Helsinki and other codes that in part originated from the Nuremberg Trial constitute guidelines in human biomedical research. Yet, the implicated physicians and investigators can not be held juridically liable according to these codes.

EUROPEAN UNION DIRECTIVES

The medical device industry comprehends a variety of products covering hundreds of thousands of items ranging from gauze dressings, walking canes, artificial heart valves to nuclear magnetic resonance imaging equipment etcetera. There are overall about 5500 medical device manufacturers in Europe and the diversity as well as the (increasing) number and complexity of the devices calls for legislative measures ensuring product safety and reliability.

The EEC, now known as the European Union, has since 1987 issued a series of some 25 Directives serving the dual purpose of facilitating the free movement of goods and assuring a high level of protection of public interests. These Directives all are adopted on the New Approach to technical harmonization and the Global Approach to conformity assessment and certification. As part of this program, the EEC has since June 20, 1990 issued a series of three Directives covering all medical devices (19-23). These Directives state that clinical investigations must be performed in accordance with the Declaration of Helsinki and the assessment shall comply with an appropriate plan to confirm or refute the manufacturer's claims for the device. Furthermore, the investigation shall include an adequate number of observations to guarantee the scientific validity of the conclusion and be performed in circumstances similar to those found under normal conditions of use of the device. All adverse events shall be recorded. The competent authorities must be informed about any device related malfunctioning or deterioration in performance characteristics. Such reporting is mandatory and upon receipt of this information, Member States shall take the ne-

cessary steps to inform the manufacturer. Furthermore, manufacturers must notify the competent authorities about any technical or medical reason leading to systematic recall of a device. Data on manufacturers recalls or adverse events shall be registered in a European database accessible to the competent authorities of the Member States. Lastly, where a Member State ascertains that devices may compromise the health or safety of the patients it shall take all appropriate measures to withdraw such devices from the market or prohibit that they are being placed on the market. Member States shall immediately inform the Commission and the other Member States of any such measures.

The first of the Directives covering Active Implantable Medical Devices was implemented on January 1, 1993 (21). A transitional period until December 31, 1994 was provided for by the Directive during which any preexisting national control (in force on December 31, 1992) may coexist with the harmonized Community system. The Medical Devices Directive was issued on June 14, 1993 and was to take effect within all Member States on January 1, 1995 (22). Yet, until June 13, 1998, Member States were to accept the placing on the market and the putting into service of devices which conformed to the national rules in force on December 31, 1994. This Directive incorporates medical equipment such as joint replacements, bone cement, intraocular lenses, heart valves, breast implants et cetera. The Directive classifies medical devices into four categories (Class I, IIa, IIb, and III) depending upon the risk associated with its use, the vulnerability of the part of the human body where the product is applied, and its wear time. Subsequently, the Directive has been subject to amendments including a reclassification of breast implants as well as shoulder, hip, and knee prostheses for joint replacements from category IIb to III. The third Directive covering In Vitro Diagnostic Medical Devices was accepted by the European Parliament and by the Council on October 27, 1998 (23). This Directive became active within the Member States on June 7, 2000. However, until December 7, 2003, Member States allowed marketing of devices which conformed to the national rules in force on December 7, 1998.

The Member States incorporate each of the three Directives into the national legislation. Each State is supposed to inform the Commission and other Member States of the Notified Bodies designated for carrying out the tasks of assessment and verification of medical devices. The Notified Body and its staff is not to be the designer, manufacturer, supplier, installer, or user of the devices which they inspect, nor the authorized representative of any of these persons. They may not be directly involved in the design, construction, marketing, or maintenance of the devices, nor represent the parties engaged in these activities.

LEGISLATION IN DENMARK

Before the European Union Directives were issued, the regulation on medical devices was sparse and embodied certain items such as contraceptive devices, radiographic equipment, and liquids for contact lenses. With the enactment of the law covering Medical Devices on June 6, 1991 with subsequent amendments, a systematic regulation in this field was initiated. The Medical Devices Directive became active on January 1, 1995 and the Active Implantable Medical Devices came into force on March 15, 1995 through two ministerial orders issued by the Ministry of Health. The In Vitro Diagnostic Medical Devices Directive came into force on June 7, 2000. The Department of Medicines Inspection and Medical Devices was constituted on August 1, 1997 under the Danish Medicines Agency. This office is responsible also for the market surveillance of medical devices and manufacturers of such products. The Ministry of Health and the Danish Medicines Agency are the competent authorities and on November 2, 1995 the Danish Medical Devices Certification (DGM) was designated Notified Body.

The Danish Institute for Health Technology Assessment was constituted on August 15, 1997 under the auspices of the Ministry of Health as an independent, state-financed institute in the National Board of Health. The evaluation performed by this Institute focuses on four main areas, i.e. technology, economy, patients, and organisation to support decision making.

Research ethical committees have resided since 1978 (24). Yet, it was not until the enactment of the law covering the Research Ethical Committee System and Biomedical Research Projects on June 24, 1992 that physicians performing research involving human subjects became juridically liable. An application in support of a trial involving human subjects must be approved by the local or central research ethics committees. Subsequently, the law on Research Ethical Committee System and Biomedical Research Projects has been slightly modified on several occasions. The Danish Medical Association adopted the Ethical Regulations for Physicians on September 24, 1989. Later these regulations have been amended.

A council dealing with complaints about health care professionals engaging in patient care, examination, and treatment (including experimental) was established on January 1, 1988. In order to ensure patients information and informed consent to treatment the law covering patients' legal rights was enacted on July 1, 1998 taking effect from October 1, same year.

LEGISLATION IN SWEDEN

The first regulative step on medical devices was initiated with the enactment of the law of May 7, 1975 covering inspection of factory sterilized articles for single use for medical purposes. On July 1, 1993, this regulation was supplemented by the Medical Devices Act and the Medical Devices Ordinance. This legislation applies to all medical devices and basically it states that a medical device must achieve its intended purpose as specified by the manufacturer and pose no unacceptable risk to neither patients nor medical staff. As Sweden entered the European Union on January 1, 1995, the Medical Devices Directive became active. The Active Implantable Medical Devices Directive came into force on April 22, 1994. Along with the enactment of the latter Directive, a regulation concerning manufacturers obligation to report incidents and near incidents with CE-marked medical devices came into force. The In Vitro Diagnostic Medical Devices Directive became active on June 7, 2000.

The Regulation on the Responsibility for Medical Devices in Health Care of May 1, 1995 is in part based on other statutes and it specifies who is responsible for the use, checking, maintenance, safety, etcetera of various medical equipment utilized by health care personnel. Since the Act on Health and Social Care was introduced about twenty years ago it has been amended numerous times. Patients' rights to information and informed consent to treatment are acknowledged in these amendments along with the obligatory reporting of accidents and near incidents to the National Board of Health and Welfare. The regulation of January 15, 1937 known as lex Maria announced the mandatory reporting of hospital inflicted patient injuries to the National Board of Health and Welfare as well as the local police. Since September 1, 2001 through an internal reorganisation process the authority responsibility for medical devices is divided between the Medical Product Agency and the National Board of Health and Welfare. The Medical Products Agency, Semko AB, and SP-Certification are Notified Bodies.

The Swedish Council on Technology Assessment in Health Care was instituted in 1987 under the auspices of the Ministry of Health and Social Affairs and on July 1, 1992 it was established as an independent society. For various medical specialities, the quality of medical therapy has been accumulated in medical databases for up to a couple of decades. As of yet the National Board of Health and Welfare funds approximately 40 such registers. The Medical Access & Result System (MARS) under the auspices of the National Board of Health and Welfare serves the dual purpose of performing register based follow up and publishing State of the Art Information.

The Swedish Medical Association adopted the Ethical Regulations for Physicians on June 8, 1968. Though no national law covering ethical issues on biomedical research has been endorsed by legisla-

tion, every regional district has through decades had a research ethical committee affiliated with the local university school of medicine. Besides, most hospitals have an ethics committee. The council entitled Hälso- och Sjukvårdens Ansvarsnämnd has subsisted since 1980 and this office analyzes and decides on complaints about health care professionals.

LEGISLATION IN NORWAY

The regulation on medical devices was initiated with the Registration and Control of Single-Use Medical Devices that came into force on January 1, 1983. Once in effect this Regulation suspended a Royal Decree issued 24 years earlier. Through signing the European Economic Area (EEA) Agreement, Norway embraced the European Union regulations on medical devices. Following the Norwegian EEA treaty, the Regulation concerning Registration and Control of Single-Use Medical Devices was adjusted on December 2, 1994 and on June 14, 1998 it became obsolete except for the section covering inactivated humane tissue. The Medical Devices Directive and the Active Implantable Medical Devices Directive became active on January 20, 1995 and the In Vitro Diagnostic Medical Devices Directive on June 7, 2000.

After an internal reorganisation process in the spring of 1993, the Department of Pharmaceutical Services was established under the Norwegian Board of Health. This Department is responsible also for the regulatory affairs concerning manufacturers of medical devices, as well as the Notified Bodies within this area. Power is delegated to the Norwegian Board of Health as Competent Authority and National Contact Point for the Medical Devices Vigilance System. Any device defect or failure must be reported to the Norwegian Board of Health, Database for Reported Events. In the case of electromedical equipment, the supervisory authority is held also by the Norwegian Directorate for Product and Electrical Safety. For any manufacturer or vendor of medical devices with business address in Norway, registration in the Register of Medical Devices, Manufacturers, and Distributors is compulsory. The Norwegian Board for Testing and Approval of Electric Equipment, Det Norske Veritas, and the Scandinavian Institute of Dental Materials are Notified Bodies.

On November 13, 1998 a proposition concerning the rights of patients was approved on a meeting of the Ministers of the State. No council dealing with patients' complaints has been endorsed by legislation in Norway, but the proposition of November 13, 1998 acknowledges patients' rights to file such a suit. Furthermore, the proposition recognizes the establishment of regional independent institutions with no authority, but upon request it shall provide patients with information and counseling in the engagement with the health care system.

The Norwegian Medical Association adopted the Ethical Regulations for Physicians in 1961 with amendments in 1997. No national law concerning medical research ethics committee has been enacted. Yet, in 1985 five regional research ethics committees were established, and subsequently hospital ethics committees faded out. Three central research ethics committees among other domains covering medicine were constituted in 1990. Neither the central nor the regional medical research committees have authority, but it is considered infeasible to perform clinical investigations without approval from the medical research committee.

LEGISLATION IN FINLAND

The regulation on medical devices was introduced with a decree covering the quality of contraceptives in September 1, 1975. In 1991 the circular concerning Mandatory Type Testing and Control of Medical Equipment was issued. This regulation embodied electromedical apparatus, and the objective was to ensure that a device complied with the specifications as stated by the manufacturer. Later this law has been abrogated and substitute regulations are enclosed in the Medical Devices Act of 1994. The Medical Devices Act of December 28, 1984 with subsequent amendments was abolished with the Act of December 29, 1994 concerning Medical Devices. As Finland joined the European Union on January 1, 1995 the Medical Devices and the Active Implantable Medical Devices Directives took effect from the date of entrance. The In Vitro Diagnostic Medical Devices Directive became active on June 7, 2000.

The National Agency for Medicines in its present form was established on March 1, 1993. This organ is responsible for the regulation of medicines, medical devices, and blood products as well as the Notified Bodies within this area. Furthermore, the Agency is engaged in the regulatory matters of research activities, keeps an Adverse Incident Register, and among other publications has issued the Normative Guideline on Clinical Investigation of Medical Devices on December 11, 1997. The VTT Automation was designated Notified Body on April 28, 1995.

The National Research and Development Centre for Welfare and Health (STAKES) was founded in 1992. This centre monitors and evaluates the operation and development of social welfare and health care and performs research and development in these fields. Furthermore STAKES also houses the Office for Health Care Technology Assessment (FinOHTA) that was established on January 1, 1995. The National Board of Medicolegal Affairs licenses health care professionals and is responsible for the supervision, disciplinary matters, and restrictions on as well as withdrawal of such licenses.

The law of August 17, 1992 concerning the Status and Rights of Patients came into force on March 1, 1993 and it relates to patients' rights to information and consent to treatment. Moreover, establishments providing medical care must have a patient ombudsman, whose duties are information and counseling – if necessary in assisting filing a complaint about the treatment provided. On June 26, 1998 the National Ethical Committee for health care was established with an act amending the Act on the Status and Rights of Patients. Subsequent amendments have later been performed. The law on Medical Research was constituted on April 9, 1999 taking effect from November 1, the same year. It also contains a section on Ethical Committees stating that every of the 20 hospital districts must have at least one Ethical Committee.

THE BONELOC® CEMENT

The development of Boneloc® was initiated in 1986. The financial support of the project was recommended by the National University Hospital in Copenhagen as well as the National Board of Health in Denmark. The cement was manufactured by Polymers Reconstructive A/S, Farum, Denmark and provided as an integrated package, mixing, and delivery system consisting of a vacuum-packed, double chamber pouch (15). Boneloc® was supposed to be less toxic as it contained a relatively small proportion of the monomer methylmethacrylate (MMA). Compared to a standard cement the leakage of MMA from Boneloc® was smaller after three weeks, however, the total amount of released monomers extracted from Boneloc® within the same time period was higher (25). Relative to standard polymethylmethacrylate (PMMA) bone cements, Boneloc® demonstrated lower exothermic temperatures during the polymerization process (26, 27). Whether a lower polymerization temperature and an alteration in leakage of monomers from Boneloc® may have any clinical relevance concerning the risk of aseptic implant loosening remains to be substantiated.

On July 12, 1990, Boneloc® was introduced at the department of orthopedic surgery, at the National University Hospital, Copenhagen, Denmark (28). Preceded by non-human experimental testing including toxicological studies (29-32), this orthopedic department established the use of this cement during an observation era that ended late 1990. During this period 62 primary hip arthroplasty patients were implanted with Boneloc®. In January 1991 Boneloc® was put on the market and subsequently it was considered the cement of choice in this department until the use was abandoned in November 1993. Apparently accepting that only limited clinical experience was available more than 30 hospitals and clinical centers in

Denmark instituted the use of Boneloc®, and approximately 3100 patients were implanted with this cement in the period from 1991 to April 1995. The manufacturer sold 7085 Boneloc® units in Denmark. Two or more units of the cement are commonly utilized in each patient.

As a consequence of some early failures seen with the first generation of Boneloc® in a few Danish orthopedic departments, a conference joined by 29 orthopedic specialists representing 22 out of a total of 42 domestic orthopedic departments and clinics was arranged by Polymers Reconstructive A/S in Farum on January 29, 1993. It was the opinion of the attendants that the use of the Boneloc® cartridge system caused some difficulties. Yet, the participants concluded it to be too early to draw any major conclusions about the future clinical applicability of the Boneloc® cement. Imaginably, the issues regarding the operating of the cement to some extent were user related in that it was questionable whether the instruction manual concerning the mixing, handling, and timing of application was followed strictly in the clinical setting. Such inapt management could compromise the mechanical strength of the cement seriously. In 1994 the manufacturer introduced the second generation of Boneloc® which partly compensated for the experienced mixing problems.

Boneloc® was used extensively in other Scandinavian countries as well. In Norway the employment of Boneloc® was accepted on April 11, 1991 by the Committee for Single-Use Medical Devices, and this bone cement was registered accordingly to the Regulations for Registration and Control of Single-Use Medical Devices. No pilot study was ever initiated. Approximately 3600 Boneloc® units were sold in this country, and about 1300 patients with total hip (33) and around 300-400 with knee replacements were implanted with this cement until the distributor withdrew from the Norwegian market in May 1994.

Based on an analysis of 8579 Charnley prostheses in 7922 patients from the Norwegian Arthroplasty Register, Havelin et al. notice the revision rate of the femoral and acetabular components implanted with Boneloc® to be 8.7 and 4.0 times higher, respectively, than for the components with high-viscosity cement without antibiotic (34). Boneloc® was applied in 760 acetabular and 764 femoral components of the 8579 implanted prostheses. Relative to the high-viscosity cement without antibiotic, the revision rate for the low-viscosity cement without antibiotic was 2.4 and 0.5 for the femoral and acetabular components respectively. In May 1994 the conclusion of the Havelin et al. study was available and the data were presented in October 1994 at the Norwegian Orthopedic Association meeting in Oslo (35). On May 18, 1994 the Norwegian Orthopedic Association as well as the Norwegian Board of Health in Norway were notified about the performance of the new bone cement. The Norwegian distributor and the Danish manufacturer of Boneloc® were informed as well. Subsequently the Norwegian distributor resigned from marketing Boneloc®. Though confronted with the critical data from the Norwegian Arthroplasty Register, Polymers Reconstructive neither informed the National Board of Health in Denmark nor did the company withdraw the bone cement from commercial distribution. Upon receipt of the knowledge of the clinical outcome of Boneloc® from patients enrolled in the National Arthroplasty Register, the Norwegian Orthopedic Association in 1994 recommended that the use of this cement should be stopped (36). In July 1994 through a mainly nationally distributed journal published by the Norwegian Board of Health the problems with Boneloc® as documented by Havelin et al. were released. The National Board of Health in Denmark is one of a few foreign subscribers to this very journal. It was not until April 28, 1995 that the Norwegian Board of Health through the Medical Devices Vigilance System issued the crucial information about Boneloc® to the relevant boards in the remaining Scandinavian countries as well as the European Union Member States. Conceivably, this delay was attributed partly to the fact that the journal that owned all rights to the material accepted for publication from the Havelin et al. investigation did not grant permission to releasing the pertinent data until then. Yet, as the vigilance report was released, the data revealed that the percentage revision rate had increased from 4.5 after two years to nearly 10 at the three years follow-up in March 1995 for the Boneloc® cemented prostheses, whereas a comparable decrease in survival rate was not documented in the control group.

In Sweden, based on a randomized study involving 30 patients (25), it was concluded that Boneloc® demonstrated inferior fixation properties, and subsequently (1995) the Swedish Orthopedic Association disbanded this cement.

In Finland, Boneloc® was introduced as an experimental therapy in the autumn of 1990. No pilot study was performed before an estimate of 1000 patients were implanted with this cement in the period from February 1991 until late 1994. The first study published about human subjects receiving Boneloc® revealed inadequate mechanical qualities of the cement (37). Yet, the conclusion of this investigation was based on a restricted number of observations. In late 1994 the Finnish Orthopedic Association urged the Finnish distributor to cease retailing Boneloc®. Subsequently the distributor resigned from marketing this cement in Finland. No official statement was released by the Finnish Medicolegal Affairs to discontinue the use of the Boneloc® cement.

As of April 6, 1995 Polymers Reconstructive A/S withdrew from the market worldwide. The Boneloc® cement was distributed worldwide in approximately 50 countries, and the cumulated sales enumerated 30,694 units.

DISCUSSION

After medical devices are placed on the market, it is possible to pool extensive information about the products through clinical trials and reports from individual physicians. Few studies note a low failure rate with Boneloc® (28, 38-40). Generally it appears clear today, that in combination with other designs than the Exeter prosthesis Boneloc® leads to higher rates of aseptic loosening, relative to conventional bone cement (25, 33, 34, 36, 37, 41-44). The femoral component of the Exeter prosthesis allows for distal movement by creep (33). It is hypothesized that this design may in part compensate for inferior mechanical properties of a bone cement (33). Correspondingly, relative to conventional bone cement, Boneloc® demonstrates inferior fixation characteristics in total knee arthroplasty also (45).

Boneloc® had been studied extensively through laboratory testing (14, 15, 29-32, 46, 47). In Denmark Boneloc® was initially evaluated clinically not employing radiographic assessment modalities such as dual-energy X-ray absorptiometry (DEXA) (48) or roentgen stereophotogrammetric analysis (RSA) (12, 49-52) known to be of value in revealing early signs of prosthetic loosening. Essentials such as a pilot study, randomization, or provision of a control group were not included to assess the outcome of an experimental therapy. The existing legislation neither outlined nor required such prerequisites and the applicable European Union Directive was not active at the time of introduction of this new implantable device. After Boneloc® was introduced to commercial distribution in the beginning of 1991, most of the orthopedic centers in Denmark, Norway, and Finland could be criticized as they were more than quick to employ this new cement without having reasonable caution for proven clinical safety and effectiveness. On the other hand, it could be stated that in January 1993, the manufacturer of Boneloc® as well as representatives from most of the involved orthopedic departments did not hesitate to openheartedly discuss potential problems with the bone cement, the use of which the clinicians had evidently advocated a couple of years earlier. In reconsideration, any consensus statement concerning a future role of any experimental treatment appears best solved under the auspices of the applicable medical society or the National Board of Health without interference of the implicated manufacturer.

The Danish manufacturer of Boneloc® was provided with the rel-

evant data of the Havelin et al. study in mid 1994. Contrary to the legislation at that time in Sweden, the manufacturer was not required to notify the Danish National Board of Health according to the existent Danish law. The incentive of the manufacturer of Boneloc® to inform the relevant boards about the inferior performance of the cement appeared at best unsatisfactory. Furthermore, despite of being faced with the serious data, the bone cement manufacturer did not recall the product in 1994, but hesitated and retreated from the market on April 6, 1995.

On several occasions the Danish National Board of Health was informed about problems encountered with the cement. It seems troublesome that the Board of Health was ignorant and nonrespondent to the critical data about Boneloc® presented in October 1993 and October 1994 at the Danish Orthopedic Society meetings in Copenhagen (53-55). In 1993 the Danish study at the two year follow-up revealed that 13 of 43 (30 percent) patients implanted with Boneloc® subsequently underwent revisions because of aseptic loosening of the prostheses (53). After three years the loosening rate increased to 16 of 43 (37 percent) (54). In March and November 1994, the Board was notified explicitly about the overall outcome of this study and potential problems with the cement (55). Even then the Board of Health apparently opted for an observant attitude. It appears uncertain when the Danish Board was faced with the controversies with Boneloc® as reported by the Norwegian Board of Health in July 1994. The information about the device was obviously not appropriately coordinated within the Danish Board, and the logistics appear in part flawed because of compromised internal communication procedures (55). The Danish National Board of Health never initiated a scrutiny process of Boneloc® neither did the Board require a withdrawal of the device from the market. Established on the existing federal law the Board concluded it to be infeasible to file a lawsuit against the company or take other legal action in order to impose a recall of the device from commercial distribution. The fundamentals of the Danish regulations covering product liability (June 6, 1989) and safety (May 18, 1994) are not to cover issues involving medical devices and based on this legislation it appears questionable who is liable (if anybody) in the provision or use of inadequate performing medical technology. The Medical Devices Directive came into force in Denmark on January 1, 1995. According to the transitional provisions of the Directive, Member States until June 13, 1998 should accept marketing of devices which conformed to the rules in force in their territory on December 31, 1994. The Directive does not specify whether manufacturers of defective devices placed on the market before January 1, 1995 can be forced to recall such medical technology during the transitional period. The Danish National Board of Health at that point of time obviously did not consider itself to be authorized to take any action concerning the employment of Boneloc®. In case absence of legislation was the particular factor for the passive policy one would hypothesize that the incentive subsequently for establishing guidelines in this field was strong. The Danish National Board of Health on July 2, 1999 released a statement on implementation of new interventions in health care. The Swedish National Board of Health and Welfare in September 1996 and the Finnish National Agency for Medicines in December 1997 issued guidelines on clinical investigation of medical devices.

In retrospect, the national legislative regulation on medical devices in most of the Scandinavian countries was inappropriate until the European Medical Directives were ratified. In part this has compromised the ability of the separate National Boards of Health to apply a dynamic and rigorous policy concerning potential device related failures leading to malfunctioning and complications. Yet, it appears unclear whether an inadequate legislative support can be conceived as an exclusive justification for the hesitant course of most of the National Boards of Health in the Nordic countries. Retaining sovereign authority in health care matters such boards have the ultimate responsibility at any (early) time to regulate medical device technology. It appeared highly questionable whether the boards endeavored this assignment in the Boneloc® case.

The issues raised prompt the question whether an equivalent incident could occur today. A few years ago in France, 56 incidents of spontaneous fracturing of ceramic zirconia femoral heads occurred between 13 and 27 months after total hip replacements. All these ceramic heads were fabricated by Saint-Gobain Ceramiques Avancees Desmarquest in France. Worldwide the company fabricates 80% of the zirconia femoral heads distributed through about 50 manufacturers of arthroplasty prostheses. Initially it was believed that the failure was limited to one serial batch, but soon it became evident that several batches were affected. An investigation performed by the French health department indicated that the fracturing was associated with a modified fabricating technique performed by Saint-Gobain in the early 1998. On July 26, 2001, the French Agency of the Medical Safety of Health Products through the vigilance system notified the European Union Member States as well as other implicated countries about the occurrence. In order to cease further mishaps it was decided to ban marketing, distribution, and export of the applicable zirconia batches. A recall of the batches was initiated through the various manufacturers. Saint-Gobain produced about 200,000 zirconia ceramic femoral heads in the period from 1998 until the vigilance report was issued.

The ceramic femoral head was a Class IIb device and it was CE-marked according to the Medical Devices Directive. Subsequently, shoulder, hip, and knee joint implants have been reclassified to category III. The incident implied potential shortcomings of the Directives. Once CE-marked, medical devices are available throughout the Union. After the expansion to 25 Member States this economic area now constitutes above 450 million citizens. Such immediate and universal access to a plethora of potential patients and consumers certainly calls for properly designed clinical trials, competent regulatory measures, and a cautious implementation of new medical technology. The EEC is a supranational organisation able to enact legislation directly on Member States. Based on the principles of the New Approach, the EEC is faced with the dual task of coordinating and harmonizing national regulations on medical devices to dismantle barriers to trade and at the same time providing patients and users with reliable, effective, and safe products. Such a complex and prestigious program is not able to operate flawlessly at all times and it should be realized, that at least initially some degree of hesitation is inherent to any new legislation. Furthermore, a deviating course is more than likely to occur occasionally, despite the fact that the Member States have reached conformity. However, these considerations do not justify that the recommendations on clinical assessment of medical devices contained in the Directives are vague. They do not recommended a minimum of individuals to be assessed nor employment of parameters indicative of the long-term outcome or survival of surgical implants neither a prerequisite such as randomization in order to minimize bias and systematic error. The current European Union program is unable to warrant the long term reliability and effectiveness of CE-marked devices and likely this objective emerges infeasible for any approval program. A too rigorous policy is liable to cause a negative impact on the development of new medical technology and ultimately deny patients useful innovations.

After the Directives have been implemented, it is illegitimate to withhold unfavorable pivotal information about a device during shorter or longer periods of time. Now manufacturers are required to report incidents and near incidents with CE-marked medical devices. In that respect, a Boneloc® reoccurrence seems unlikely, despite logistic problems with the vigilance system have been described (56). The objective of the vigilance system is to improve the safety and efficacy of medical devices by reducing the risk of the same type of adverse event being repeated. The quality of the system relies primarily on the awareness and compliance of the medical profession, manufacturers, competent authorities, and patients. The

spontaneous prosthesis fracturing case demonstrated an adequately operating system. As indicated, any delays or flaws in recording and reporting of adverse incidents may, however, compromise the safety and health of even numerous patients.

Vigilance also is contained in the manufacturer's wider post-marketing surveillance obligations under the European Union Directives. As part of the quality assurance system, the manufacturer must establish and keep up to date a systematic procedure to review experience gained from devices in the post-production phase. This obligation is often poorly understood and frequently underestimated by the industry (56). Furthermore, data on recalls or adverse events are registered in a data bank available to the Member States. Yet, the Directives do not provide for freedom of information on all clinical data of separate devices. Unless the medical companies or the competent authorities comply, it is impossible to obtain information about clinical data, performance status etcetera supporting the premarket approval application that assigned a device with a CE-mark. Though it is possible for potential vendees to request data of the kind, systematic recordings of all clinical data including post-marketing performances should be available for clinicians, competent authorities, and public at large. The need for equivalent databases on various medical implants is imperative in order to establish the base for benchmark testing.

The ultimate goal in medical outcome research is to improve treatment and at the same time minimizing the risks. Yet, new medical technology does not necessarily represent a breakthrough which will be of long-term benefit. When interpreting the outcome of new (CE-marked) devices a sceptical approach is always mandated and further evaluation often will be needed. After results of (randomized) trials are accessible, multicenter studies, and subsequent longer-term monitoring of larger patient populations should pursue (57). Once such adequate and valid tests have been successfully passed, devices can be allowed general access. Such strategies reduce the risk of compromising the health or safety of a large number of patients.

Upholding high professional standards in medical outcome research mandates more than evaluation through randomized controlled trials, a step-by-step introduction, as well as establishment of clinical databases. The final implication of recalling Boneloc® will (hopefully) direct physicians to disregard interests in personal preferences and resist the pressure from industry, politicians, press, colleagues, and patients to rush toward implementing new medical innovations extensively. This legacy is intangible and difficult to control by any regulation – including the European Union Directives on medical devices.

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