Introduction of Brachytherapy to a German Catheterization Laboratory:
How to Meet the Regulations Within a Reasonable Time Frame

SIGMUND SILBER, M.D., and ARMIN SCHNEIDER, PH.D.

From Dr. Müller Hospital, München, Germany

Presently, approximately 100 catheterization laboratories in the United States and over 20 in Europe perform intracoronary brachytherapy. In Germany, the first patients were treated with intracoronary afterloading in 1998. In this article, we describe our experience with the approval processes for clinical research and for routine use with the Novoste BetaCath™ system. First, all major German authorities and laws involved in this process are named and explained. Then, the required steps for obtaining the license for research and routine use are described. Finally, we compare three systems (BetaCath™ Novoste, Gamma-IVT™ Cordis, and BetaMed™ Boston Scientific) regarding handling for security and maintenance checks, dosimetry verifications, and leakage testing. With the increasing amount of data, obtaining the license for clinical routine use is possible in Germany within a reasonable time frame, provided the brachytherapy device has a CE certificate. (J Interven Cardiol 1999;12:473–476)

Introduction

Intracoronary brachytherapy is increasingly used in cardiac catheterization laboratories for prevention and treatment of de novo lesions, restenotic lesions (without stents) and in-stent restenosis.[1–10] Presently, approximately 100 cath labs in the United States and over 20 cath labs in Europe perform intracoronary brachytherapy with various systems.

In Germany, the first patients were treated with intracoronary afterloading in 1998. In November 1996, we initiated the process for approval to participate in several international multicenter studies. In addition, we received the license for clinical routine use in July 1999.

The purpose of this article is to describe our experience with the approval process, which is inherently different from regulatory considerations in the United States.[11,12] Although in Germany the final license is issued by regional (state) authorities, licensing in other German states can be extrapolated from our experience in the state of Bavaria. We assume that this article will make it easier for others to find the most efficient way to get approval for clinical research and/or clinical routine use.

Address for reprints: Sigmund Silber, M.D. FACC, Professor of Medicine, Dr. Müller Hospital, Am Isarkanal 36, D-81379 München, Germany. Fax: +49-89-74215131, e-mail: silber@med.de

License for Clinical Research

Table 1 defines the acronyms used for the authorities and laws mentioned in this text. Table 2 lists the authorities and paragraphs involved in the approval process for clinical research, and figure 1 depicts their temporal sequence. Clinical studies can be conducted with devices with or without the CE mark. Of course, it is easier to get approval for research using a CE-certified device. If the brachytherapy device is not CE approved or used for purposes other than those described in the CE approval, two additional steps must be taken: (1) insurance according to MPG § 17 Pt. 1 Nr. 9 (required by the Ethics Committee), and (2) a special device approval by the LfAS, according to the MPG § 17 Pt. 6 (required for LfU). Then, two independent institutions will review the project: an Ethics Committee and the BfS. The Ethics Committee follows the general rules according to the existing data and possible

Table 1. Glossary of Acronyms Used for Major Authorities and Laws Involved in the Process of Licensing Intracoronary Brachytherapy in Germany

AMG	Arzneimittelgesetz	Medical Product Law
AtDeckV	Atomrechtliche Deckungsvorsorge-Verordnung	Regulation for the Right of Nuclear Security Provision
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte	Federal Institute for Drugs and Medical Products
BfS	Bundesamt für Strahlenschutz	Federal Office for Radiation Protection
EC	Ethikkommission	Ethics Committee
LfAS	Landesamt für Arbeitsschutz	State Office for Maintenance of Industrial Health and Safety
LfU	Landesamt für Umweltschutz	State Office of Environmental Protection
MPG	Medizin Produkte Gesetz	Medical Product Law
StrlSchV	Strahlenschutzverordnung	Regulation for Radiation Protection

risks for patients and critically approves the informed consent form according to the guidelines for Good Clinical Practices (GCP). It is important to emphasize that usually Institutional Review Board (IRB) approval alone is not sufficient. Not all Ethics Committees are accredited according to MPG § 17 Pt. 7 and listed at the BfArM.[6] The BfArM (in Berlin) must be notified according to § 40 Pt. 1/1/Nr. 6 of the AMG, about the clinical trial, with an application for a specific filing number. Working with encapsulated brachytherapy systems (e.g., the Novoste [Novoste Corp., Norcross, GA, USA] or Cordis systems [Cordis Corp., Miami, FL, USA]) makes this step easier than applying for open radioactive systems (like liquid-filled balloons)[13] that require a pharmacological-toxicological examination (risk of inadvertent injection).

Table 2. Institutions and Paragraphs Involved in the Licensing Process for Research and Routine Use of Intracoronary Brachytherapy in Germany

	Research	Routine Use
Device Prerequisites	No Specific	CE Certificate
LfU approval:		
StrlSchV §3	+	+
StrlSchV § 41/42	+/−	−/+
EC approval	+	−
BfS approval	+	−
Insurance for EC MPG § 17/1/9	+	−
Insurance for Atomic Law AtDeckV § 15	+	−
Insurance for personal liability	+	+
LfAS—MPG § 17/6 (if not CE certified)	+	n/a
LfAS—StrlSchV §76	+	+
Fire department approval	+	+

For abbreviations, see Table 1.

The BfS is a federal institution located in Neuherberg, Munich. The experts of the BfS will calculate all radiation questions involved and report directly to the LfU whether the project including the assumed dosage calculations are reasonable and feasible.

The LfU is the key institution that gives the final approval. The LfU collects all of the above-mentioned

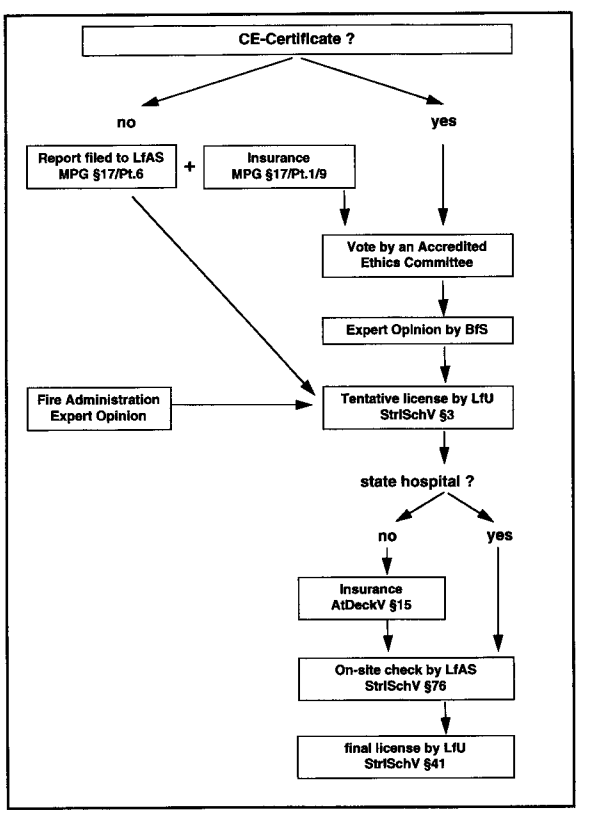

Figure 1. Flow chart for licensing approval for intracoronary brachytherapy to do ethical research. Acronyms are explained in Table 1; for more details, see the text.

reports and requires an additional insurance policy per patient of 1 Mio DM according to Atomic Law At-DeckV § 15 (without a cap). This very high insurance is necessary in hospitals that are not run by the government, such as all community, city, denominational, and private hospitals.[14] Therefore, this insurance is needed by most hospitals in Germany, except the majority of university hospitals. If all papers meet the requirements of the LfU, they will issue a StrlSchV (Regulation for Radiation Protection) § 3 license, enabling the cath lab to receive the radioactive sources and verify the dose rates.

Before final approval according to StrlSchV § 41,[15] the LfAS must come to the cath lab and check the devices for security and maintenance as well as dose rates according to StrlSchV § 76.

License for Clinical Routine Use

The LfU issues the license for clinical routine use according to StrlSchV § 3 and StrlSchV § 42 (Table 2). Clinical routine use can only be approved for CE-certified devices. According to the definition of the clinical routine use, approval by the Ethics Committee, BfS, or BfArM is not required. Furthermore, the tremendous insurance rate according to the Atomic Law is not necessary. Of course, the performing physicians need an additional personal liability insurance policy. After StrlSchV § 3 has been issued by the LfU, the LfAS must check the devices in the cath lab (StrlSchV § 76) before final approval by the LfU according to StrlSchV § 42.

All radiation safety and fire department regulations have to be obeyed for research or for routine use. In our cath lab, no constructional changes had to be made for using beta radiation with the Novoste™ System. For gamma radiation, safety issues are a concern.[8] Because no one in Germany has used gamma radiation in a cath lab, it is not known whether a lead shield alone is appropriate or if constructional changes will be necessary.

Follow-up Requirements

After receiving the license for clinical research or routine use, some specific regulatory procedures must be obeyed: security and maintenance checks, dosimetry verifications, and leakage testing.

Security and Maintenance Checks. According to StrlSchV § 76, the integrity of the devices (i.e., their security and maintenance) must be checked by the LfAS every time a new transfer device is delivered. As an alternative, the § 76 check may be performed at the manufacturer's site by an approved company. If a transfer device is used for several years, this check has to be repeated on an annual basis (Table 3).

Dosimetry Verifications. According to the guidelines for quality assurance, the dosimetry has to be verified every time a new source is delivered. Although some institutions may accept the dosimetry measurements provided by the manufacturers at delivery, most will insist on a local verification. If the source is used for more than 6 months, dosimetry verification becomes a requirement after this time (Table 2).

Leakage Tests. According to StrlSchv § 75, leakage tests must be performed annually, preferably after exposure to water with 50°C for 4 hours. In general, the leakage test is performed by the manufacturer and will be accepted at delivery by most institutions. The next leakage test is due 1 year after delivery. If the radioactive source is exchanged within 1 year, no leakage tests are required on-site.

Comparison. To compare the burden of different follow-up tests in the real world of intracoronary afterloaders, we evaluated three different systems (Table 4). Since it is the policy of Novoste to exchange the transfer devices every 6 months, maintenance checks must be performed according to these intervals. Although the half-life time of strontium-90 used in the Beta-Cath™ system is approximately 29 years, Novoste recommends exchanging the radioactive sources every year. Therefore, dosimetry verification must be performed 6 months after delivery of the pellets. With this concept for exchanging transfer devices and pellets, leakage tests must not be performed on-site.

With regard to the Gamma-IVT™ system, various factors must be taken into consideration. In contrast to Novoste, Cordis simultaneously exchanges the ra-

Table 3. Requirements to Verify Device Integrity and Dosimetry at Delivery and During Follow-up Usage According to German Laws and Guidelines for Quality Assurance

	At Delivery	Follow-up
Security and maintenance check	+	Annually
Dosimetry verification	+	Every 6 months
Leakage test	(manufacturer)	Annually

Table 4. Time Intervals for Various Checks

	Beta-Cath™ (Novoste)	Gamma-IVT™ (Cordis)	BetaMed™ (Boston-Scientific)
Security and maintenance check	Every 6 months	Every 4 weeks	Annually
Dosimetry verification	Every 6 months	Every 4 weeks	Every week
Leakage test	–	–	–

Time intervals for various checks required in Germany with regard to the half-life of the isotopes and the policy of various manufacturers for exchanging the sources and transfer devices. Security and maintenance checks must be performed every time a transfer device is swapped. Surprisingly, leakage tests do not have to be performed with either system due to the exchange policy of the companies.

dioactive sources and the transfer device every 4 weeks. Therefore, security and maintenance checks must be conducted once a month. The monthly exchange of the transfer devices is related to the short half-life time of iridium-192 of 74 days; and dosimetry verification must be performed every month. On-site leakage tests are not necessary.

The sources of the BetaMed™ system (Boston Scientific Corp., Watertown, MA, USA) are exchanged every week due to the very short half-life time of yttrium-90 of 64 hours. Therefore, on-site dosimetry verifications must be conducted on a weekly basis. Fortunately, the transfer device (a sturdy afterloader) can remain for a longer period of time, so the security and maintenance checks are necessary only once a year (Table 4).

Conclusion

The licensing process for approval to conduct clinical research with intracoronary brachytherapy is painful and time consuming. With the increasing amount of data, obtaining the license for clinical routine use is possible within a reasonable time frame, provided the brachytherapy device has a CE certificate.

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