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# Off-Label Use of Medical Products in Radiation Therapy

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Report of AAPM Task Group 121

August 2010

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ISBN: 978-1-888340-96-9  
ISSN: 0271-7344

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Published by  
American Association of Physicists in Medicine  
One Physics Ellipse  
College Park, MD 20740-3846

## Task Group I2I Members

**Bruce R. Thomadsen**

*Department of Medical Physics, University of Wisconsin, Madison, Wisconsin 53705*

**H. Thompson Heaton II**

*Hagerstown, Maryland 21740*

**Shirish K. Jani**

*Department of Radiation Oncology, Sharp Memorial Hospital, San Diego, California 92123*

**Jeffery P. Masten**

*Radiation Oncology, Rapid City Regional Hospital, Rapid City, South Dakota 57709*

**Mary E. Napolitano**

*Atlanta Research and Development, Elekta, Inc., Norcross, Georgia 30092*

**Zoubir Ouhib**

*Department of Radiation Oncology, Lynn Regional Cancer Center, Delray Beach, Florida 33484*

**Chester S. Reft**

*Department of Radiation Oncology, University of Chicago, Chicago, Illinois 60637*

**Mark J. Rivard**

*Department of Radiation Oncology, Tufts University School of Medicine, Boston, Massachusetts 02111*

**T. Tydings Robin**

*Consultant, Theragenics Corporation, Buford, Georgia 30518*

**Manny Subramanian**

*Department of Research and Development, Best Medical International, Inc., Springfield, Virginia 22153*

**Orhan H. Suleiman**

*Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland 20993*

**Contact information:**

Bruce R. Thomadsen

Department of Medical Physics

University of Wisconsin

L1-1105 Wisconsin Institutes for Medical Research

1111 Highland Avenue

Madison, Wisconsin 53705

[thomadsen@humonc.wisc.edu](mailto:thomadsen@humonc.wisc.edu)

Voice: 608-263-4183

FAX: 608-262-2413

## **Abstract**

Medical products (devices, drugs, or biologics) contain information in their labeling regarding the manner in which the manufacturer has determined that the products can be used in a safe and effective manner. The U.S. Food and Drug Administration (FDA) approves medical products for use for these specific indications that are part of the medical products labeling. When medical products are used in a manner not specified in the labeling, it is commonly referred to as off-label use. The practice of medicine allows for this off-label use to treat individual patients, but the ethical and legal implications for such unapproved use can be confusing. Although the responsibility and ultimately the liability for off-label use often rest with the prescribing physician, the medical physicist and others may also be responsible for the safe and proper use of the medical products. When these products are used for purposes other than which they were approved, it is important for medical physicists to understand their responsibilities.

In the United States, medical products can only be marketed if officially cleared, approved, or licensed by the FDA; they can be used if they are not subject to or specifically exempt from FDA regulations, or if they are being used in research with the appropriate regulatory safeguards. Medical devices are either cleared or approved by FDA's Center for Devices and Radiological Health. Drugs are approved by FDA's Center for Drug Evaluation and Research, and biological products such as vaccines or blood are licensed under a biologics license agreement by FDA's Center for Biologics Evaluation and Research. For the purpose of this report the process by which FDA eventually clears, approves, or licenses such products for marketing in the United States will be referred to as "approval."

This report summarizes the various ways medical products, primarily medical devices, can legally be brought to market in the United States and includes a discussion of the approval process, along with manufacturers' responsibilities, labeling, marketing and promotion, and off-label use. This is an educational and descriptive report, and does not contain prescriptive recommendations. This report also addresses the role of the medical physicist in clinical situations involving off-label use. Case studies in radiation therapy are presented. Any mention of commercial products is for identification only; it does not imply recommendations or endorsements by any of the authors or the AAPM.

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## I. INTRODUCTION

Medical products, devices, drugs or biologics must be cleared, approved, or licensed by the U.S. Food and Drug Administration (FDA) prior to being legally marketed in the United States. The terms clearance, approval, and licensing depend on the type of medical product, and which of the FDA Centers conducts the review. Medical devices, the main subject of this report, are either cleared or approved by FDA's Center for Devices and Radiological Health (CDRH). Drugs are approved by FDA's Center for Drug Evaluation and Research (CDER), and biologics are licensed by FDA's Center for Biologics Evaluation and Research (CBER).

In order to introduce a medical device into commerce, medical device manufacturers must register to notify the FDA at least 90 days in advance of their intent to market a medical device. The FDA review process may simply involve filing what is known as a Premarket Notification or 510(k), named after Section 510(k) of the *Food, Drug and Cosmetic Act* (FDCA). It allows the FDA to determine whether the device is equivalent to a predicate device that has already been placed into one of the three safety classification categories. If the proposed use of the device is determined to be a significant risk that may pose a potential for serious risk to the health, safety, or welfare of a subject, a Premarket Approval (PMA) application may be required before the medical device can be marketed.

Unless the medical product is exempt from FDA regulation, collection of human research data during premarket clinical trials must be performed under an Investigational Device Exemption (IDE) for medical devices, or under an Investigational New Drug (IND) application for drugs or biologics. This is the clinical research phase of medical product development, and such human research is highly regulated. Human research data collected during this phase are submitted to the FDA in a separate filing known as a PMA for a medical device, New Drug Application (NDA) for a drug, or a Biologics Licensing Agreement (BLA) for a biologic.

Institutions conducting clinical trials must have the research approved by an institutional research board (IRB). An IRB is a panel at a facility, comprised of medical and non-medical persons, to review applications for human investigational studies. The Board weighs the safety of the study with the benefit that might come from the study. The protocol, consent procedure, and evaluation methodology must all be approved for any research using human subjects.

When medical products are used in a manner that is different than specified in the labeling, or used for medical indications that are not specified in the labeling, this is referred to as "off-label" use. Such use is not necessarily illegal or improper. Rather, such use has not been evaluated by the FDA, and is authorized under a licensed physician's right to practice medicine. In order to practice medicine in the United States, one must be licensed in the appropriate state jurisdiction and properly trained and credentialed. In general, the use of medical products such as drugs or devices must be performed by, or under the supervision of, licensed practitioners/qualified individuals. The purpose of this report is to provide for the medical physicist an appreciation of the responsibility and potential liability when a medical product is used consistent with its labeling or when it is not.

Section 6 of this report discusses recommended actions by the medical physicist in situations involving off-label use. This is an educational and descriptive report, and does not contain prescriptive recommendations.

This report intends to discuss some of these issues briefly. For more detailed information, refer to appendix C and the FDA website, [www.fda.gov](http://www.fda.gov). This website provides current and extensive information on how medical products, including devices, drugs, and biologics, are regulated.

## 2. REGULATORY AGENCIES

In order to possess and use radioactive materials, the facility or user must be licensed either by the Nuclear Regulatory Commission (NRC) or an Agreement State. While medical products may be used by the medical community for other than the approved indications under the practice of medicine, radioactive materials that have been licensed for a specific use cannot be used for other uses. The unauthorized use of radioactive material is strictly prohibited and could result in fines and other penalties. There is an excellent discussion of this by Glasgow related to NRC requirements for intravascular brachytherapy (IVBT) sources.<sup>1</sup> The NRC and agreement states have two major responsibilities with respect to new brachytherapy sources. The first is structural integrity, ensuring that sealed sources and devices can safely contain radioactivity under the conditions of their use. The second is that the users be qualified to safely use these radioactive materials. This is done by licensing the user and the site where the radioactive materials are used. The NRC has no position on off-label use of an approved device. Off-license use is strictly illegal.

FDA's regulatory focus is on the manufacturer of the medical product, namely on the documentation the manufacturer submits to show that the product can be used for its intended use. If the medical product is approved by FDA for marketing, conditions of use are specified in the medical product labeling (Information for Use, product inserts, advertising material, etc.). Compliance with the specific labeling instructions is an assurance that the medical product is considered by FDA to be safe and effective for the specific medical indications. After FDA approval, certain events must be reported, as discussed in appendix C2.6 (and summarized in Table II in appendix C).

## 3. LEGAL ISSUES

Stated most simply, the term “off-label” is a regulatory description of the use of a medical device or drug. In the words of one court, it is “a legal status, not a medical fact”.<sup>2</sup> It can be safely said that the majority view in the United States is that off-label use of a drug or device is proper as long as certain criteria are satisfied.<sup>3</sup>

Although “off-label” has a relatively simple meaning from a legal standpoint, considerable linguistic confusion has been generated by the attempt to understand what “off-label” uses in fact are. Beck and Azari describe the problem succinctly in their law review article:<sup>4</sup>

Unfortunately, terminology problems persist. It is common parlance to say that a drug or device is FDA “approved” for a given use if that use appears on the label. The converse proposition, however, (which is decidedly not true) would be that such products are “unapproved” for all unlabeled uses. This erroneous concept of approved use takes on derogatory connotations if divorced from a regulatory context, as would be the case in an informed consent discussion. To

those unfamiliar with FDA regulation, a group that includes most patients, unapproved suggests “disapproved”—that is, some affirmative determination by FDA that an off-label use is actually too unsafe or too risky to appear on labeling. “Off-label drug use by oncologists is quite common” but people “mistakenly equate...the off-label categorization of these uses...with lack of evidence of effectiveness.”<sup>5</sup> A recent notable example of a court falling into precisely this error is *Proctor v. Davis*,<sup>6</sup> in which the court repeatedly refers to off-label use as “unauthorized” by FDA, when, as previously discussed, the agency lacks and has disclaimed any power to allow or disallow off-label use. FDA ordinarily looks to a manufacturer’s intended uses when considering how a drug or device is to be marketed and labeled. Thus, absent a labeled contraindication, unindicated uses cannot be considered unapproved; they simply have not been reviewed at all. [This appears to be the situation in the *Proctor* case, no application was filed with the FDA concerning the off-label use at issue. 682 N.E.2d at 1209-10. Indeed, FDA refused the manufacturer’s request to add adverse reactions relating to that precise off-label use to its labeling shortly before the incident at suit. *Id.* at 1210. For unexplained reasons the manufacturer’s request and FDA’s refusal of it were excluded from evidence in *Proctor, id.*, and the court took the position that the manufacturer was liable for not including in its labeling the information that FDA had refused to allow. *Id.* at 1214.]

There are other ways of understanding the legal nature of “off-label.” One could describe “off-label” as a silent label. “Off-label” has more accurately been termed “extra-label” use. It simply means that a product is being used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely.<sup>7</sup>

As we pointed out in the beginning of this document, the FDA has never had authority to regulate the practice of medicine. This is fundamental to understanding the term “off-label.” Physicians may use legally marketed drugs or devices in any manner that they believe, in their professional judgment, will best serve their patients.<sup>4,8</sup> The Legislative History section of appendix D discusses this in more detail.

Another area of confusion arises out of the investigational or experimental use of devices and drugs. An “off-label” use is not “investigational” simply because a label is silent on the proposed use. “In the legal context of informed consent litigation, the potential for confusion is compounded because this description also misuses FDA terminology with a precise regulatory meaning. There are particularized informed consent regulations governing investigational drugs and devices, but these regulations do not, and should not, apply to off-label use.”<sup>4</sup> The appendices to this report explore different aspects of the investigational use issue more fully.

### 3.1 Liability Analysis

The discussion above demonstrates that off-label use of medical devices is an accepted part of the practice of medicine. In a clinical setting, there are no triggers that would separate off-label use from the regular use of a medical device in the context of liability analysis. IDE and IND trials are excepted here. A full analysis of a potential claim arising out of the off-label use of a device is beyond the scope of this report. However, to assist the medical physicist in appreciating the nature of the legal issues involved in such a professional liability claim, appendix D offers an overview and supporting authorities. For an in-depth review of the parts of a negligence claim written specifically for medical physicists, see Shalek and Gooden, *Medical Physicists and Malpractice*, Medical Physics Publishing, 1996.<sup>9</sup>

### 3.2 Other Legal Issues

The above sections focus on the legal issues arising from harm to a particular patient. The FDA and other regulatory agencies also focus on the “systematic encouragement” of off-label use. Systematic encouragement of a practice that is currently “off label” should be preceded by the manufacturer modifying the labeling to include the “off-label” use after proper approval processing through the FDA.

Systematic encouragement of off-label use such as marketing efforts by manufacturers and companies can also be subject to review by the Department of Justice (DOJ). For example, Spivak<sup>10</sup> identifies on-going DOJ efforts in 2008 investigating and prosecuting cases of illegal off-label marketing. He indicates that, according to published reports, there are upwards of 200 pending qui tam (i.e., whistleblower cases) cases involving allegations of off-label promotion by healthcare companies.

In some cases, companies have settled the criminal charges and civil allegations related to their marketing practices. Remedial actions have included the prohibition of promotion for unapproved or off-label use of drugs or devices and compliance training for promotional speakers and sales representatives. Other remedial actions include prohibiting company staff from responding to requests for off-label information unless the request is made in writing. The cases also signal that the DOJ continues to closely scrutinize those activities considered non-promotional, such as support for medical education and responses to unsolicited requests for information. Spivak also indicates that not only are distribution of drugs of interest to DOJ, but also devices including software.

In November 2007, the Department of Health and Human Services and the DOJ published “Health Care Fraud and Abuse Control Program Annual Report for FY 2006.”<sup>11</sup> That document discussed their accomplishments in investigating and prosecuting health care fraud schemes. Investigations included efforts in hospital fraud, pharmaceutical fraud, fraud by physicians, as well as fraud by other practitioners. Off-label issues were identified only in the pharmaceutical fraud areas and no cases involving medical physicists were cited in efforts involving fraud by other practitioners. Another example of off-label activity involving legal issues was reported by *The Wall Street Journal*.<sup>12</sup> The report indicated that the DOJ is investigating the off-label use of a Medtronic Inc., implant for promoting bone growth, bringing government scrutiny of such unapproved uses to the heart of the \$189 billion per year medical-device industry.

Based on the above, medical physicists should carefully examine their role, if any, in efforts to promote the off-label use of a drug or device, and should consider obtaining legal advice if uncomfortable.

## 4. MANUFACTURER RESPONSIBILITIES

Manufacturers are allowed to promote a medical product only for the specific indications for which it was cleared, approved, or licensed. Manufacturers are prohibited from promoting off-label use of their products unless they are reporting information as part of an approved clinical trial. Experts in the medical field may report on the off-label use of a drug or device through publications, conferences, and other professional forums; there is a difference between the reporting of observations for an approved use, reporting observations for off-label use, and reporting observations from clinical trials. Although many medical societies require the presen-

ters to declare the off-label or research uses (and any conflicts of interest such as financial interests with the product being promoted), the manufacturer has very little control over enforcement of society requirements or individual speakers.

#### **4.1 Guidance to Industry Regarding Reprint Practices**

If a physician or health care professional specifically requests a report or publication already available in the peer-reviewed literature, a manufacturer may be able to provide unaltered copies of the publication discussing the off-label use for educational purposes but not for promotional purposes. Manufacturers are not allowed to distribute unsolicited information for marketing their product for an unapproved indication.

FDA guidance and regulations are constantly being revised and good reprint practice is no exception. Section 401 of the *FDA Modernization Act*, which provided conditions under which journal articles or reference publication concerning off-label usage could be distributed ceased to be effective on September 30, 2006. At the time of printing, the FDA has published guidance for industry<sup>13,14</sup> in order to provide the current views of the agency. This guidance recognizes that truthful and non-misleading information from journal articles and reference publications concerning off-label usage can be of benefit to the public health when appropriately distributed to health care professionals.

The agency lists recommendations concerning the types of reprint/articles/reference publications that would and would not be considered appropriate along with the manner in which the agency considers the distribution appropriate. For example, an appropriate type of article and dissemination is a scientific journal article published in accordance with an organization's peer-reviewed procedures being distributed following a related technical discussion. An inappropriate type and dissemination would be if a highlighted and abridged version of the same reference was being distributed in the exhibit hall. The guidance document lists more information for review by the interested reader.

#### **4.2 Knowledge of Off-Label Usage**

Sometimes a manufacturer may become aware of anecdotal results obtained for off-label use of the device. The manufacturer may decide, based on this new information, to conduct a formal clinical trial in order to obtain the necessary clinical data to submit to FDA for approval of a new indication. Since clinical trials are expensive, the manufacturer may also decide that the expanded use through the practice of medicine is sufficient and may decide not to apply for a new indication. It may simply be a business decision to allow the practice of medicine to adopt the new practice. In this scenario, a medical product may be used legally for a commonly accepted but unapproved indication.

Debate also exists concerning the responsibility of the manufacturer with knowledge of prevalent off-label use of the product when the manufacturer decides not to actively promote the new indication or to conduct a clinical trial for approval of the new indication. While the physician always has the prerogative to use an approved device in an off-label manner, debate ensues as to the obligation of the manufacturer to undergo the expense and manpower required to conduct the necessary clinical trials and to submit the off-label usage for approval by the FDA. Since the FDA does not regulate the practice of medicine, the off-label usage without active promotion by the manufacturer would not fall under the FDA's jurisdiction.

Solid medical rationale should support the off-label use of a drug or device. “Off-label use does not imply an improper use and certainly does not imply an illegal use or contraindication based on evidence”.<sup>15</sup> For example, for patients with “orphan diseases” (i.e., less than 200,000 patients diagnosed per year), drugs are often used off-label because of a lack of incentives for the manufacturer to develop additional indications for small markets. The legal and regulatory environment surrounding off-label use is an area that continues to evolve. In some areas, in particular the treatment of cancer, off-label use is often considered necessary in order to provide quality patient care. For example, a 1991 study conducted by the General Accounting Office reported that approximately 60% of cancer patients were treated using at least one off-label drug.<sup>16</sup>

Off-label indications may sometimes result in the discovery of new applications for existing drugs. In fact, it has been stated that well over 50% of drug innovations were developed as a result of use of drugs in off-label indications by practicing clinicians rather than by the drug industry.<sup>17</sup> Although the manufacturer can compile the published off-label use of a product and provide that to FDA at periodic intervals, the healthcare provider is not obligated to provide the information to the manufacturer or publish the results unless death or serious injury results. Hence for practical and business reasons, it may be difficult for the manufacturer to monitor all the off-label uses of their products. In a recent guidance document,<sup>13</sup> the FDA does specifically encourage the manufacturer to seek approvals for new uses of approved products. See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> for the article “Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices,” last accessed 3 November 2009.

## **5. BILLING AND REIMBURSEMENT ISSUES**

Reimbursement can be approved for Medicare and Medicaid patients, as well as by third party insurance carriers, for indications that have not been approved by FDA, but this issue sometimes can be confusing. Medical facilities should consult their local Medicare Carrier before using a device off-label with the expectation of some reimbursement. See appendix E for more details on reimbursement.

## **6. MEDICAL PHYSICIST’S RESPONSIBILITIES AND DOSIMETRY ISSUES FOR OFF-LABEL USE**

Many radiation-producing devices or radiopharmaceuticals that have labeling restrictions also have some form of dosimetry associated with the standard uses. Very often, the dosimetry for the approved uses fails to reflect true dose information, but rather provides simple standardization for consistent applications between patients. The standard treatments may deliver a mostly consistent dose, such as in the case of the Cordis IVBT system, which originally required ultrasound measurements of the treatment geometry and patient anatomy for calculation of dose to a defined location in the vessel wall. On the other extreme are treatments such as <sup>89</sup>SrCl<sub>2</sub> injections for metastatic bone pain that specified a fixed activity for all patients. In each case, the

approval process established that the procedure was safe as tested during the formal clinical trials. However, the meaning of safety varies, especially for patients with refractory disease where the approved indication may be palliation.

Off-label use puts the user outside the officially approved bounds of safety and effectiveness, and also where the dose to the patient may be unknown, unknowable, or unexpected. Consider the problem using the Novoste™ Beta-Cath™ source to treat vessel diameters larger than those specified in the labeling. Several problems could be encountered. First could be lack of data for longer treatment distances. Since the vendor only specifies treatments for a range of vessel diameters, dose information beyond that range may not be included. Extrapolating doses beyond existing data for beta sources can introduce considerable errors because of the rapid gradient in the dose with distance. Even in cases where the dosimetry factors may be known and the treatment time calculated at some greater distance, there could be unexpected consequences. For example, the treatment time could become very large because the fraction of the radiation penetrating to the greater distance may be small. If the catheter is not centered in the vessel, the dose to the closest point in the vessel wall could be several times that normally delivered, while the dose on the farthest point might fall beyond the range of the beta particles and be severely underdosed. The treatment could fail either by injuring the proximal side or failure to deliver an adequate dose distally.

Some off-label uses of devices pose no dosimetric issues for a medical physicist, for example, using a linear accelerator to treat mitral valve replacements. Assuming successful addressing of motion problems, the dose distribution can be known as well as when treating cancer. Notwithstanding the absence of a dosimetric question, the FDA may consider such irradiation as significant risk, such as in this case.

Most treatment modalities that can be used off-label are outside of the normally encountered situations. For new devices and drug-based therapies, the manufacturers are usually required to provide training to the critical staff, including medical physicists. During this training, the medical physicist learns the indications and limitations for use, which leaves anything else as off-label use. Medical physicists should become familiar with the approved uses so as to recognize when an application would be off-label. The physicians involved should recognize off-label situations and call that fact to the physicist's attention early in discussions about the patient. Anything unusual about the patient's treatment should initiate a check by the medical physicist as to whether the treatment would be off-label. This can be verified by simply seeking written answers from the manufacturer for clarifications. Linear accelerators as a product have general approval to treat cancers and *certain benign diseases*, although some have not included benign diseases in their labeling. For units that include treatment of benign diseases in their labeling, benign diseases for which there is not information in standard textbooks raises flags about the therapy being off-label.

Judgments on the usage of a device for a proposed off-label situation must be made for each particular case. Examples of some items that could be considered include the following:

- Will the changes from usual treatment produce changes in the dose distribution?
- If the dose distribution will change, can the new dose distribution be calculated or otherwise determined?
- Might any new dose distribution affect the patient's treatment detrimentally?
- Could a new dose distribution produce unintended consequences?

Very likely, the answers to at least some of these questions will not be available and cannot be found in time to address the given treatment. Calculation of doses in unusual situations or from new devices often proves challenging to research institutions with specialized resources, and is not something that most clinics could perform. Those difficulties notwithstanding, expected changes in dosimetry and possible results must be considered before performing the off-label treatments. It is prudent to contact someone who was involved with the original dosimetry to solicit an opinion regarding these issues.

The off-label use of a device can have both desirable and non-desirable results. When desirable results are achieved, it usually occurs when the usage of the device has been considered thoroughly for the off-label situation by all members of the treatment team. Using a device off-label will also require a plan of action, understood by the whole team, to be executed in the event of a non-desirable situation. Issues can range from discomfort to a serious consequence, since no clinical trials were performed under the same clinical situation. As an example, consider the Novoste Beta-Cath system being used for a long lesion. These kinds of lesions usually require a “stepping method” to cover the whole length. The Novoste catheter is placed in the vessel and left in place until both segments are treated. This will amount to having the catheter in place for a longer period of time, approximately twice the time of a short lesion. The presence of the catheter might create a serious discomfort for some patients and, if not taken seriously by the cardiologist, could potentially lead to serious consequences. The stepping method might require an overlap or gap of the sources between the two segments. The clinical consequences are not well understood because of the lack of clinical data and might be more critical when there is curvature of the vessel within the area to be treated. This uncertainty could lead to serious overdose or underdose in the overlap or gap regions. The clinical results of these unusual situations can only be evaluated with time. From the regulatory side, the concern would be that the stepping method could lead to a possible medical event (e.g., an overdose or underdose at the match line).

One has to be aware that while the purpose of the off-label use is well intentioned, sometimes the results can cause serious problems for the patient. Since off-label use deviates from the formal labeling instructions, it may shift liability of the product from the manufacturer elsewhere, eventually to the institution. One will have to be prepared and act upon non-desirable outcomes.

Some examples of steps the medical physicist should take in proposed off-label treatments include:

- Ensuring that, if possible, appropriate dosimetry calculations are in place at the time of treatment for each case to avoid “on-the-fly” dosimetry calculations.
- If dosimetry for the proposed off-label use raises new safety and effectiveness issues for treating patients, informing the rest of the clinical team, preferably in writing.
- Ensuring that any new safety and effectiveness concerns raised by the dosimetry calculations or other physics-related issues are communicated to the treating physician to be included in the Informed Consent Form for the patient (see the discussion in appendix D).

## 7. CASE STUDIES

The material in the following case studies is not intended to be guidance on how to treat patients in an off-label manner. Rather it is intended to provide guidance on the types of concerns the medical physicist should consider when told by the physician how the device will be used off-label for treatment of an individual patient. These case studies provide only some of the details of the type of information the medical physicist should consider, and they are not intended to be an all inclusive discussion. In these case studies, it is assumed that a medical decision has been made to treat an individual patient using a medical device in a specific off-label manner. Any physics concerns of the proposed treatment should clearly be conveyed to other members of the clinical team, in writing. As with all off-label uses of a device, it is a medical decision that the use of the device for that individual patient is in the best interests of treating that patient. In all of the case studies, just as for conventional treatments or human-use research trials, it is assumed the physician has provided an Informed Consent Form, including specifics of the treatment, for the patient to consider.

### 7.1 Intravascular Brachytherapy

#### 7.1.1 Background

To treat individual patients, intravascular brachytherapy (IVBT) devices were frequently used off-label (see section 7.1.2 for more information on their labeling). The first medical products to show significant results in a clinical trial for the reduction of in-stent restenosis following balloon angioplasty were IVBT sources, although they were eventually superseded to a great extent by drug-eluting stents. During the development stages of IVBT, the radiation sources used in the coronary vessel clinical trials included seed trains (with<sup>17,18</sup> and without<sup>19,20,21,22,23</sup> inter-seed spacing), wires,<sup>25-38</sup> radioactive stents,<sup>40,41,42</sup> radioactive liquid-filled balloons,<sup>43,44,45</sup> radioactive gas-filled balloons,<sup>46</sup> and balloons impregnated with radioactivity.<sup>47,48</sup> In addition, there were peripheral vascular trials<sup>49</sup> using an high dose-rate (HDR) <sup>192</sup>Ir remote afterloading system and external beam therapy for patients with A-V shunts.<sup>50</sup> Most of the device sources were delivered to the intended treatment site by first inserting a catheter through the femoral artery and using this catheter to move the source for treatment of predetermined dwell times to deliver the prescription dose at the prescription point. The intended use for all approved coronary IVBT devices is to treat coronary in-stent restenosis with a prescribed dose of radiation (which may depend on vessel diameter) at a prescribed point.

There is a different regulatory paradigm for brachytherapy sources used in the vascular system for treating disease from that for conventional brachytherapy sources used to treat cancer. Since brachytherapy sources were used before 1976 to treat cancer, they were grandfathered in when the Medical Device Amendments (MDA) were passed. When new interstitial brachytherapy sources or auxiliary devices were developed, the normal regulatory route to market was to claim they were substantially equivalent (SE) to, and had the same intended use as, a legally marketed pre-amendment predicate device. Additionally, the manufacturers had to state that any technological changes to the device did not raise any new safety and effectiveness issues for its intended use. This allowed manufacturers to file premarket notification under section 510(k) of

the Act as discussed in 21 CFR 807.81-807.100. This also meant that the typical operations the physicist performed, such as quality assurance, source calibration, treatment planning, etc., did not violate labeling.

The situation with IVBT sources was quite different. First, the FDA determined that the use of radiation to treat disease in the vascular system was a new intended use of radiation. Second, the FDA determined that the use of radiation to treat disease in the vascular system was a significant risk (SR), i.e., an FDA-approved IDE was needed to gather clinical data. Thus for IVBT devices, a PMA was needed before the product could be legally marketed.

### *7.1.2 Approved labeling for intravascular brachytherapy devices*

In gathering the clinical data for IVBT devices, the device is investigated under a very specific set of conditions including prescription dose, prescription point, range of source activities, etc. Hence, the only information FDA can evaluate for the safety and effectiveness of the device is the clinical and non-clinical data gathered during the IDE study and submitted in the PMA.

The Instructions for Use (IFU) for the three FDA-approved IVBT systems for treating in-stent restenosis (units by Cordis, Novoste and Guidant) summarize the information obtained during the clinical trial. Most of the information in these IFUs pertains to the clinical trial and typically most of the dosimetry is in an appendix. All three systems are only approved for treating in-stent restenosis of specified lesion lengths, specified vessel diameters, and use a specific prescription dose at a specific prescription point. Only one system is approved for stepping or source pull-back. Any other use of these systems for treating vascular disease is off-label use of the system. The dosimetry parameters of the three approved IVBT systems for treating in-stent restenosis are found in their IFUs.<sup>51,52,53</sup>

### *7.1.3 Specific IVBT dosimetry issues not included in original labeling*

One of the important considerations if an IVBT source is to be used off-label is to be able to calculate the dose rate from the source at any clinically relevant point. In particular, the dose rate at the prescription point is needed to calculate the dwell time. Further, one needs the dose-rate distribution if the dose at the vessel wall for a non-centered source is desired, the dose along a curved vessel, the dose in the margins of the treatment volume, effects of stent attenuation, effect of contrast media, and the dose maximums and minimums created by pullback. In addition to the references cited above, dosimetry from IVBT sources is discussed in the following articles.<sup>54-65</sup>

Some examples of conditions when it may be desirable to use an IVBT source off-label or for physical conditions not considered in the dosimetry for the original labeling include: dose at bifurcations,<sup>66</sup> effect of plaque on dose rate,<sup>67,68</sup> effect of contrast media on dose rate,<sup>69,70</sup> effect of vessel curvature or source movement,<sup>71</sup> treating peripheral vessels,<sup>72</sup> treating SVG,<sup>73,74</sup> dosimetry based on intravascular ultrasound (IVUS),<sup>75</sup> source pull-back during treatment,<sup>76,77,78,79</sup> use of radiation treatment planning software,<sup>80</sup> use of well chambers to calibrate sources,<sup>81,82</sup> and quality management for IVBT.<sup>83</sup>

## 7.2 Radiolabeled Microsphere Brachytherapy

Microspheres labeled with  $^{90}\text{Y}$  have been approved for treatment of cancer in the liver. The microspheres are injected intra-arterially into the hepatic artery. The microspheres flow with the blood until they reach the capillaries, where, being too large to fit, they lodge in the capillary mouths. This therapy selectively delivers dose to the tumors because they receive almost all their blood supply from the hepatic artery, while the liver proper receives 80% of its blood supply from the portal vein. The products of two manufacturers were approved for this use.

One of the manufacturers, MDS Nordion (Kanata, Ontario, Canada), makes TheraSphere<sup>®</sup>, glass spheres, 10 to 30  $\mu\text{m}$  in diameter with an average  $^{90}\text{Y}$  labeling of 2.5 kBq per sphere. TheraSpheres were approved via a Humanitarian Device Exception H980006.<sup>84</sup> The indicated use for these spheres is: "...for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters."<sup>83</sup> The other manufacturer, Sirtex (Wilmington, MA), markets resin spheres called SIR-Spheres<sup>®</sup>. SIR-Spheres are a little larger, ranging from 20 to 40  $\mu\text{m}$  in diameter, but carry less activity per sphere, averaging about 50 Bq per sphere. These were approved via Premarket Approval Application P99065 (and supplements S001 and S004).<sup>85</sup> The indication for use for these spheres is: "...for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine)".

Because the microspheres block the capillaries, one concern in the delivery of the treatment is that the spheres may block so much of the blood flow that the material injected no longer flows into the arteries leading to the tumors (antegrade flow) but shunts backwards (retrograde flow) and into arteries feeding other locations (of particular concern is the gastric artery supplying the stomach). The probability of filling the capillary bed depends on the number of microspheres injected.

Off-label use mostly centers around three situations: (1) using one manufacturer's product to treat the disease for which the other manufacturer's spheres were approved; (2) using radiolabeled microspheres to treat a cancer in the liver for which microspheres have not been approved; and (3) using radioactive microspheres to treat disease in other parts of the body. Each of these situations involves different issues. An additional "dosimetry" issue is that the prescription is normally in terms of activity to be injected into the liver rather than dose to the liver. Note, however, that in a recent guidance document<sup>86</sup> on microspheres the NRC specifies "For Y-90 microspheres, 'prescribed dose' means the total dose (rad or Gy). Alternatively, prescribed activity (mCi or GBq) may be used in lieu of prescribed dose. Additionally, it specifies that the written directive should include: (1) "pre-administration: the date; the signature of the AU; the treatment site; the radionuclide (including the physical form [Y-90 microspheres]); the prescribed dose/activity; and, if appropriate for the type of microsphere used, identify the manufacturer and include the statement 'or dose/activity delivered at stasis';" and (2) "after administration but before the patient or human research subject leaves the post-procedural recovery area: the date; the signature of the AU; and the total dose/activity delivered to the treatment site. If the administration was terminated because of stasis, then the total dose/activity to the treatment site is the value of the total dose/activity administered when stasis occurred and the administration was terminated. Note: The post-administration entries into the written directive are not an amendment to the written directive; rather, these entries complete the written directive."

*7.2.1 Using one manufacturer's product to treat the disease for which the other manufacturer's spheres were approved*

FDA approval for the microspheres being limited to a specific disease resulted from the clinical trials sponsored by the manufacturers to prove the safety and efficacy of their products. Because of the costs of running a clinical trial, the vendors picked a specific disease. The choices may seem arbitrary, but some reasons support the differentiation. While hepatocellular cancer often presents with disease widely disseminated through the liver, sometimes only a few, discrete foci are involved. These may be best treated with a small number of microspheres with a relatively high specific activity. Microspheres with less activity per sphere would have a difficult time getting enough product in place to deliver the dose without filling the capillary bed prematurely. On the other hand, while metastases to the liver may appear as a few nodules, very likely many smaller sites exist below the resolution of the imaging systems. In these cases, the radioactive material should cover a wide volume of the liver, suggesting a large number of lower-activity spheres. While the foregoing discussion finds basis in reasoning, no clinical data supports the arguments.

A treatment facility may have been licensed for one of the two products, and be faced with a patient having the disease specific to the other type of microspheres but without the time needed for authorization, training, and logistical setup to use appropriate microsphere product. Using the product they already have authorization for qualifies as off-label use. Before proceeding, questions to be addressed include:

- a. Will the injection likely cover the target region adequately without filling the capillary bed prematurely?
- b. How does the dose as calculated by one system compare with that of the other system. Neither product calculates the dose to the tumor, nor do they make a realistic calculation of the dose to the liver. The clinical results in the trials were tied to the calculation method used, through simple, empirical designs. Because of the difference in the distribution of the microspheres between the manufacturers' products, the empirical calculations from one manufacturer may not result in the same biological effect when used with the other product.

While the physicist and physician in a clinic may be able to estimate the probability of the adequate coverage, the question of dose equivalency between the products and between the calculational approaches remains a research topic of considerable difficulty. The estimation of the classic radiation absorbed dose is problematic with any radiopharmaceutical, and especially so in this case. The exact tumor volume treated is unknown or extremely difficult to determine, and the administered radioactivity will distribute according to the circulation. The inhomogeneity of the tumor and the microsphere distribution leads to such an extremely high uncertainty in dose estimation that it is fair to say that, at the present time, it is unknown.

*7.2.2 Using radiolabeled microspheres to treat a cancer in the liver for which no microsphere has been approved*

Many cancers metastasize to the liver and often fail to respond to conventional treatments. Clinicians may be tempted to use the radiolabeled microspheres since they have proven effective

for hepatocellular primaries and colorectal metastases. One major issue with other types of metastases concerns their vascularity. On arteriograms, the approved tumors demonstrate a marked vascularity, which is part of their biology. Other tumors often do not have this property. Infusing such tumors would likely result in little uptake of the radionuclide in the cancer and a concomitantly high dose to the liver parenchyma, potentially injuring the patient seriously.

### *7.2.3 Using radioactive microspheres to treat disease in other parts of the body*

The unique anatomy of the liver—the dual arterial supply and the partition between tumor and normal cells—provides the liver with the ideal situation for treatment with radiolabeled microspheres. However, tumors in many locations fail to respond to other therapies. Attempting to use radiolabeled microspheres in such situations takes the practitioner far afield from the clinical trials. All the issues in the two situations discussed above apply, as does the question of shunting. Many tumors exhibit bizarre vascular patterns and flow anomalies that could result in major, unexpected exposure to sensitive, normal tissues. These questions raise serious issues that need to be addressed before proceeding. While solid answers to almost any of the questions remain unavailable, the considerations must support that serious injury to the patient would be unlikely before such off-label use is undertaken.

## **8. SUMMARY**

It is important to understand the concept of off-label use of an FDA-approved medical product (device or drug), especially for the medical physicist. To have a better understanding of the implications of using a medical product off-label, it is helpful to review the role of labeling in the FDA approval process of a medical device or drug. Hence, the first part of this report and appendix C review the various processes that a device manufacturer can use to obtain premarket approval before the device can be legally marketed.

Sometimes device labeling is quite specific in what its intended use(s) encompasses. However, once a medical product is approved, even for a limited indication, as part of the practice of medicine, a licensed physician can decide to treat an individual patient in a manner not included in the labeling, and hence treat in an off-label manner. As part of the clinical team treating the patient, if the medical physicist determines that the proposed use of the medical product raises new safety and effectiveness issues, these should be communicated in writing to other team members before treating that patient. A medical physicist usually learns about what the labeling uses are for a treatment modality during the training provided by the manufacturer. During this training the medical physicist should ask for clarification about specific FDA-approved labeling indications. Any other use is considered off-label, and the manufacturer is not permitted by the FDA to promote such use. There are, however, situations where off-label use has been described in the published literature; in such cases the manufacturer may reference such studies when FDA requirements and guidelines have been followed. To make the medical physicist more aware of the relevant legal issues of treating an individual patient off-label, a summary of the legal issues is included.

Finally, two case studies of off-label use are presented. These raise some of the issues that the medical physicist should consider as a clinical team member concerned with the role of radiation and clinical implications of the proposed product for that patient, as discussed in section 6. The case studies do not represent any type of official FDA policy on the off-label use of the devices in the case studies, but are simply examples of the type of issues the medical physicist should consider when a medical product device is to be used off-label in treating an individual patient. The appropriate Center within FDA should be contacted directly if there are questions on the FDA approval process for medical devices or drugs since the information in 21 CFR will change with new congressional legislation. Information on the indications for use of approved medical products can be found through the links on the CDRH database website.<sup>87</sup>

## APPENDIX A

### Acronyms

BLA	Biologics Licensing application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CRT	Cathode ray tube
CT	Computed tomography
DOJ	Department of Justice
FDA	U.S. Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDCA	Food, Drug and Cosmetic Act
FDCAA	Food, Drug and Cosmetic Act as Amended
FUDR	Floxuridine
GRASE	Generally recognized as safe and effective
HCC	Hepatocellular carcinoma
HDE	Humanitarian Device Exception
HDR	High dose-rate
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IFC	Informed Consent Form
IFU	Instructions for Use
IHAC	Intra-hepatic artery chemotherapy
IND	Investigational New Drug (application)

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IRB	Institutional Review Board
IVBT	Intravascular brachytherapy
IVUS	Intravascular ultrasound
MDA	Medical Device Amendments
MDR	Medical Device Report
MSQA	Mammography Quality Standards Act
NDA	New Drug Application
NRC	Nuclear Regulatory Commission
NSE	Not Substantially Equivalent
NSR	Nonsignificant Risk
PMA	Premarket Approval (application)
RCHSA	Radiological Control for Health and Safety Act
RDRC	Radioactive Drug Research Committee
RTOG	Radiation Therapy Oncology Group
RSC	Radiation Safety Committee
SE	Substantially Equivalent
SR	Significant Risk
SVG	Saphenous vein grafts

## APPENDIX B

### Definitions

Black Box warning	A black frame surrounding a warning in a label to draw particular attention to it.
Labeling	Statements of all conditions, purposes, or uses for which such device is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the device is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the device can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner. [21 CFR 801.5(a)] <sup>88</sup>
Medical Device	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes. [FDCAA 201(h)] <sup>89</sup>
Nonsignificant Risk	A device which does not pose a serious risk to study subjects or others. If the sponsor believes the device does not impart significant risk, IRB approval of a study as an NSR device can be sought.
Off-label	The use of a medical product (drug or device) to treat a patient in a manner that is not consistent with the specific FDA-approved labeling.
Practice of Medicine	The authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.
Significant Risk	A significant-risk device is an investigational device that:  (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;  (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The sponsor makes the initial decision whether a device imparts significant risk to study subjects or others. If so, the sponsor obtains an Investigational Device Exemption (IDE) from FDA in addition to IRB approval.

Traceability

A property of the resulting measurement or the value of a standard, having stated uncertainties whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons, all having stated uncertainties.<sup>90</sup>

## APPENDIX C

### The Role of the Food and Drug Administration in Medical Product Approval

#### CI. Laws

FDA regulates medical products under the comprehensive Food, Drug and Cosmetic Act (FDCA), initially passed in 1938. The original three relevant statutes for radiological medical devices are the 1968 *Radiological Control for Health and Safety Act* (RCHSA), the 1976 Medical Device Amendments (MDA), and the 1992 *Mammography Quality Standards Act* (MQSA). Unlike the MQSA, the first two statutes regulate the manufacturer of the device, not the user. Users of these medical products must be licensed in the state jurisdiction that authorizes such use, FDA's responsibility is to ensure that proper use instructions consistent with submitted research data are on the product label. The radiation control statute differs from the medical device statute by holding manufacturers responsible for meeting mandatory performance standards for certain classes of electronic products, such as diagnostic x-ray, computerized tomography (CT), as well as consumer products like microwave ovens and CRT (cathode ray tube) television receivers. There are FDA statutes for other radiological medical products such as radiolabeled drugs and biologics, but drugs and biologics are governed by different sets of regulations. The main thrust of this section will be radiological medical device manufacturers as codified in 21 CFR Part 800.

The most recent statute is the *Food and Drug Administration Amendments Act* of 2007. Among the many components of the law, the *Prescription Drug User Fee Act* and the *Medical Device User Fee and Modernization Act* have been reauthorized and expanded.

#### C2. Federal Regulation of Radiation-Associated Medical Products (Specifically Medical Devices, Electronic Products, Mammography, Drugs, Biologics)

Medical devices are regulated by FDA's Center for Devices and Radiological Health (CDRH), as a medical device under the *Code of Federal Regulations* (CFR) Title 21 Food and Drugs, Subchapter H - Medical Devices Part 800. Electronic products that emit radiation are regulated under Subchapter J - Radiological Health Parts 1000–1050 while the use of mammography equipment is regulated under Subchapter I - Mammography Part 900.

Drugs or biologics may also be used in radiation therapy as an adjunct treatment, or for imaging in order to identify and assess tumor response. Most drugs are regulated by the Center for Drug Evaluation and Research (CDER) under 21 CFR, Subchapter D - Drugs for human use, while biologics are regulated by the Center for Biologics Evaluation and Research (CBER) under Subchapter F - Biologics. Sometimes regulatory responsibility shifts among these FDA agencies, e.g., FDA transferred authority for therapeutic biologic agents such as the radiolabeled monoclonal antibodies Bexxar<sup>®</sup> and Zevalin<sup>®</sup>, which are indicated for non-Hodgkins lymphoma, from CBER to CDER; ultrasound contrast agents, once regulated by both CDRH and CDER, are exclusively approved by CDER. In some situations, the designation may be less clear, such as <sup>90</sup>Y labeled microspheres, which are considered a device and therefore regulated by CDRH. If the medical product contains a radioactive material, then the facility or individual must also be licensed to possess this radioactive material, and is subject to either the requirements of an

Agreement State, or the Nuclear Regulatory Commission (NRC) under 10 CFR Part 20 - Standards for Protection Against Radiation, and Part 35 - Medical Use of Biproduct Material.

When a medical product consists of multiple FDA-regulated components, i.e., a device, drug, or biologic, then it must also be registered as a combination product 21 CFR Part 3.2 (e) with FDA's Office of Combination Products, which is not located within any Center, but is a separate Office within FDA.

### *C2.1 Medical Device Premarket Notification: 510(k)*

In order for a medical device to enter commerce, FDA first requires the filing of a premarket notification 510(k) for clearance for a medical device for which a predicate already exists. A predicate device may either have existed prior to the 1976 MDA passage or for a device which has since been cleared via a Premarket Notification [510(k)] by FDA.

For devices with no predicate, a premarket approval (PMA) application may have to be filed. This is an extensive application documenting the safety and efficacy of the device, analogous to the New Drug Application (NDA) for drugs and biologics. Additionally, in order to conduct the necessary human research, an investigational device exemption (IDE) will be necessary. This application is analogous to the Investigational New Drug (IND) application for drugs and biologics. Clearance or approval by FDA will ultimately depend on the safety and efficacy information provided.

### *C2.2 The Medical Device Premarket Approval Application*

The medical device premarket approval application, as described in 21 CFR 814,<sup>91</sup> provides the FDA with sufficient data collected during the research phase of the study, demonstrating a reasonable assurance of safety and effectiveness for its intended use. These instructions are considered part of the labeling, including instructions precautions, and possible hazards. Labeling also includes vendor training. When the medical device is used in a manner inconsistent with its intended use or deviating from the labeling instructions, it is being used off-label.

For regulatory control, the FDA classifies medical devices into three classes based on risk according to 21 CFR Part 860.3. Class I devices are subject only to general controls and are considered the safest. For this class general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Class I devices are not life-supporting or life-sustaining, and do not present a potential unreasonable risk of illness or injury.

Class II classification is for devices that currently have or which will eventually be subject to special controls. This represents a class of device for which general controls alone are insufficient to provide reasonable assurance of its safety and efficacy. This class of medical device requires the premarket notification process, i.e., section 510(k) of the act (21 CFR 807 Subpart E Premarket notification). Typical examples of such devices include teletherapy units, low-energy interstitial brachytherapy sources, and high dose-rate irradiators. A Class III device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices. Some Class II and most Class III devices will require the filing of a more extensive application known as the premarket approval (PMA) application. For more detailed information, visit the FDA website: <http://www.fda.gov>.

One pathway for premarket notification of Class II medical devices requires documentation to show that the new device is Substantially Equivalent (SE) to a predicate device on the market before the MDA was enacted. Substantial equivalence via the 510(k) process may also apply to a post MDA medical device that has been cleared or approved by FDA and the indicated use is the same as the predicate device. There is a flowchart that the manufacturer can use to make a determination if the device is SE to the legally marked predicate product.<sup>92</sup> SE does not mean identical, simply that the indication for use is the same as the predicate device, and the material and technology are the same as the predicate. If they are different, there must be sufficient data in the submission to show that there are no new safety or effectiveness issues. Usually, only non-clinical data are required in this type of submission, with only a small fraction of 510(k) submissions requiring clinical data.

Since many radiation therapy devices were already on the market prior to 1976, many manufacturers submitted 510(k) documentation showing that post 1976 device submissions were equivalent to these predicate devices. The label's information for use, or IFU, in these early submissions usually consisted of generic statements, such as treating a disease type like cancer, with no specific description of the cancer type, the anatomical location, radiation dose, number of doses, treatment schedule, dose rate, etc. These generic IFUs allowed the medical community great latitude on how the device could be used.

### *C2.3 The New Drug Application (NDA)*

The New Drug Application (NDA) for drug approval is analogous to the PMA for medical devices. For additional information we refer you to the FDA website (<http://www.fda.gov>).

### *C2.4 The Biologics Licensing Agreement (BLA)*

The Biologics Licensing Agreement (BLA) application for biologics is analogous to the NDA for new drugs and the PMA for medical devices. For additional information we refer you to the FDA website (<http://www.fda.gov>).

### *C2.5 Human Research Using an IDE or IND*

Prior to FDA clearance or approval of a medical device and for all new drugs, human research<sup>93,94</sup> may need to be conducted. One of FDA's major responsibilities is the protection of human research subjects; in order to perform such research, the sponsor or vendor needs to obtain from FDA an investigational device exemption (IDE), 21 CFR 812, for medical devices, or an investigational new drug (IND) application, 21 CFR 312, for drugs or biologics. This allows the sponsor to conduct clinical trials with the investigational medical product for very specific conditions as specified in the clinical trial protocol. This research phase is very different from the application process.

Such human research must address ethical and safety considerations, including informed consent for the research subjects. These regulatory requirements are addressed in 21 CFR 50 Protection of Human Subjects, and 21 CFR 56, Institutional Review Boards (IRBs). An IRB is a panel at a facility, comprising medical and non-medical persons, to review applications for

human investigational studies. The Board weighs the safety of the study with the benefit that might come from the study. The protocol, consent procedure, and evaluation methodology must all be approved for any research using human subjects.

#### *C2.5.1 Human research with medical devices: the Investigational Device Exemption*

If a new medical device is found to be Not Substantially Equivalent (NSE) to the predicate device or a predicate device does not exist, the method for bringing it to market is usually the PMA. Class III devices require a clinical trial with an FDA-approved IDE.<sup>87</sup> Some Class II devices also may require clinical trials and an IDE. However, the FDA may disagree with the Nonsignificant Risk (NSR) designation and require an FDA-approved IDE before the trial begins. As a specific example, initially using Intravascular Brachytherapy Therapy (IVBT) sources to treat in-stent restenosis was deemed to be not NSR by the institution's IRB. However, the FDA determined that this was a new indicated use of radiation (treating disease in the vascular system), that these devices involved new safety and effectiveness issues, and that these devices were SR, as several of the below conditions for a significant risk device apply to IVBT devices. Thus clinical trials involving these devices needed a FDA-approved IDE as well as the institution's IRB approval.

If the IRB determines that the device as it is to be used in the clinical trial is Significant Risk (SR), then the sponsor must obtain an FDA-approved IDE before the clinical trial can begin. Risk determination is based on the proposed use of the device in an investigation and not on the device alone. A significant-risk device is defined as an investigational device according to 21 CFR 812.3 (m),<sup>95</sup> as previously defined in appendix B.

Class III devices are normally brought to market by the PMA process which requires both clinical and non-clinical data to show that the device is safe and effective for its indicated use, as opposed to being merely SE as needed for premarket notification approval, e.g., 510(k). To be able to use an unapproved device in a U.S. clinical trial, the sponsor must have an FDA-approved IDE. This exempts the device from FDCA requirements that would apply to devices in commercial distribution while the device is being clinically investigated under a specific set of conditions. If non-clinical studies demonstrate that the device is safe, then the FDA-approved IDE will allow a clinical study to be conducted to show the device is safe and effective for its intended use (e.g., the clinical parameters in the clinical trial).<sup>96,97,98</sup>

The FDA-approved IDE will contain an explicit protocol to be followed during the trial; conditions for use in the protocol are very specific. In general, the IDE involving ionizing radiation products will include the following: non-clinical data including animal data, bench testing, dosimetry, specific indication for use, trial protocol, test hypothesis, statistical analysis including sample size needed to test the hypothesis, specific primary safety and effectiveness endpoints for trial, secondary endpoints for trial, patient inclusion criteria, patient exclusion criteria, informed consent form, and case report forms.

The IDEs for IVBT trials required randomized, double-blinded, placebo trials with additional dosimetry information including a well-defined prescription dose (or doses, if it was a dose escalation study) at the prescription point and dose rate per unit source output as a function of distance from the source to be used to calculate the dwell time. See Ryan for a further discussion of the regulatory requirements for approval of IVBT IDEs in the United States.<sup>99</sup>

If a device is used off-protocol during the IDE trial, the whole study can be compromised. Often the number of subjects in the trial is just sufficient to obtain the statistical power and precision necessary to validate the study hypothesis. If trial subjects are treated with an off-protocol use of the device, either the sponsor or FDA may determine that the results from these patients cannot be included in the trial. This will reduce the sample size so that the results are not statistically significant to validate the study and hence the study cannot be used for PMA approval. If the investigational product has not been previously approved, that is, if this trial is for initial approval and not for a new indication for a previously approved product, it cannot be used off-label, and, by definition, is simply the use of an unapproved, uncleared medical product.

There are other FDA mechanisms for expanded access during the IDE process for treating patients with a medical device that was not approved for the specific application.<sup>100,101,102</sup> There may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. Patients and physicians faced with these circumstances may have access to investigational devices under one of four main mechanisms by which FDA may make an unapproved device available: Emergency Use, Compassionate Use, Treatment Use, and Continued Use. These mechanisms can be utilized during a certain time frame in the IDE process if the criteria are met. FDA approval is required except in the case of emergency use. Table I (see next page) summarizes the FDA mechanisms for expanded access for treating patients with a medical device that was not approved for the specific application during the device development process.

#### *C2.5.2 Human research with drugs or biologics: the Investigational New Drug application*

To ensure the safety of human research subjects in the United States, research studies involving subjects administered drugs or biological products must be conducted under one of the following: (a) under an FDA-approved IND application unless specifically exempt from IND requirements,<sup>103</sup> (b) under a biologics license application,<sup>104</sup> or (c) under the direct oversight of a Radioactive Drug Research Committee (RDRC), an FDA-approved body charged with the review of such studies provided that they fulfill the necessary conditions.<sup>105</sup>

The use of drugs or biologics on human research subjects requires they be used under an FDA Investigational New Drug (IND) application. There are four general phases associated with drug trials: Phase I studies are generally considered safety studies, designed to test the toxicity levels of a drug in humans. Information typically gathered in these studies focuses on the metabolism and pharmacologic actions of the drug, along with pharmacokinetic and biodistribution data. Although there is no preset number of human subjects, these studies typically involve 20 to 80 subjects. Phase II studies evaluate the effectiveness of a drug for specific indications(s). These are well-controlled clinical studies that are closely monitored to determine efficacy and short-term side effects and risks. They are usually conducted on several-hundred research subjects. Phase III studies are expanded controlled and uncontrolled trials, and are intended to gather additional information regarding dosing, efficacy, and safety in order to better evaluate the benefit-risk relationship of the drug. These studies usually range from several hundred to several thousand human research subjects. Phase IV studies, not always required, are considered post-market studies, i.e., follow-up studies after a drug has been approved. These may be required by FDA for drugs that have been approved using alternative “fast-track” studies, for which limited

**Table I. FDA mechanisms for expanded access of devices under investigational trials**

Mechanism	Criteria	Time Frame
<p><b>Emergency Use:</b> Situations in which there is a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study.</p>	<ul style="list-style-type: none"> <li>• life-threatening or serious disease or condition;</li> <li>• no alternative; and</li> <li>• no time to obtain FDA approval.</li> </ul>	<p>Emergency use of an unapproved device may occur before an IDE is approved.</p>
<p><b>Compassionate Use:</b> Allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group.</p>	<ul style="list-style-type: none"> <li>• serious disease or condition, and</li> <li>• no alternative.</li> </ul>	<p>Compassionate use can occur during the clinical trial.</p>
<p><b>Treatment Use:</b> An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggest that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.</p>	<ul style="list-style-type: none"> <li>• life-threatening or serious disease,</li> <li>• no alternative,</li> <li>• controlled clinical trial, and</li> <li>• sponsor pursuing marketing approval.</li> </ul>	<p>Treatment use can occur during the clinical trial.</p>
<p><b>Continued Use:</b> FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA.</p>	<ul style="list-style-type: none"> <li>• public health need or</li> <li>• preliminary evidence that the device will be effective and there are no significant safety concerns.</li> </ul>	<p>Continued use occurs after the completion of the clinical trial.</p>

data were collected, or for which long-term side effects may be suspected but not proven. These may involve large numbers of patients.

Drugs of interest to the medical imaging community may be non-radioactive contrast agents employing contrast-enhancing elements such as iodine or gadolinium. Safety issues associated with these drugs are usually toxicity related because of the large amounts used. Radiolabeled drugs, unless specifically designed as a radiotherapeutic, usually have such low pharmacologic doses that they exhibit no pharmacologic effect in humans. The safety concern is usually the radiation dose from the associated radionuclide.

FDA regulations and guidance are in a perpetual state of change, so for the most current information please go to the official FDA website (<http://www.fda.gov>).

### C2.5.3 Human research using a radioactive drug research committee (RDRC)

One class of research with radiolabeled drugs does not require that it be conducted under an IND. However, certain conditions must be met. These drugs must be conducted under an FDA-approved RDRC. In order to use a radioactive drug on human research subjects in an RDRC-supervised study, that drug must be generally recognized as safe and effective (GRASE), and the research conducted must be basic science. If a radioactive drug meets RDRC criteria, an IND is not required.

To qualify as GRASE, radiolabeled drugs must meet two specific criteria, the first relating to the pharmacologic dose and the second to the radiation dose. The first criterion specifies that the mass dose of the radiolabeled drug to be administered must not be known to cause any clinically detectable pharmacologic effect in human beings. This definition assumes *a priori* that the drug in question has no clinically detectable pharmacologic effect on humans; consequently, this criterion rules out first-in-humans testing under RDRC authority. The second criterion for radiolabeled drugs to be GRASE involves radiation safety and requires that human subjects receive the smallest radiation doses practical to perform the study and that the radiation doses the subjects receive from a single study or receive cumulatively from several studies conducted within a 1-year period do not exceed the regulatory dose limits. For the whole body, active blood-forming organs, lens of the eye, and gonads, the single dose limit is 30 mSv (3 rem), and the annual and total dose commitment is 50 mSv (5 rem); for the other organs the single dose shall not exceed 50 mSv (5 rem), and the annual and total dose commitment shall not exceed 150 mSv (15 rem).

Research overseen by RDRCs is considered basic science research when its purpose is to advance scientific knowledge and not to determine a radioactive drug's safety and effectiveness as a therapeutic, diagnostic, or preventive medical product in humans. The intent of basic science research is to obtain information such as metabolism and excretion data. Such research may also investigate the biodistribution or pharmacokinetic properties of a radiolabeled drug or its physiological, pathophysiological, or biochemical characteristics. Other types of basic science research may investigate receptor binding or occupancy, transport processes, enzyme activity, or multistep biochemical processes. Although some of the aforementioned studies may have eventual therapeutic or diagnostic implications, the initial studies are considered to be basic research within the context of the regulations.

To ensure that RDRC research complies with these requirements, the FDA vests each RDRC with the responsibility for direct oversight of the basic science research conducted at the designated medical institution, by directly reviewing and approving research protocols. The membership of the RDRC shall consist of at least five individuals, including (1) a physician recognized as a specialist in nuclear medicine, (2) a person qualified by training and experience to formulate radioactive drugs, and (3) a person having special competence in radiation safety and radiation dosimetry. The remaining committee members should be qualified in various disciplines relevant to the field of nuclear medicine, such as radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy. In addition to requiring approval by the RDRC, prospective human research study subjects must also be reviewed and approved by the IRB.

Each RDRC is required to submit to the FDA an annual report summarizing all research conducted under its authority by January 31 of each year for the previous calendar year. This

information includes a list of the members of each RDRC, the number of studies conducted by each committee, and, for each study, the study title, names of the investigators, radiolabeled drug(s) used, the pharmacologic and radiation doses administered, and the age and gender of each participating human subject. Additionally, special summaries must be submitted to the FDA immediately during the year whenever a study has human subjects under age 18 years or when the number of study subjects exceeds 30.

**C2.6 Reporting of Adverse Events for Marketed Products**

Although adverse events are collected and reported during the human research phase, once a medical product has been reviewed, cleared, approved, or licensed, the reporting of post marketed adverse events to FDA is done in a multiple of ways.

Medical Device Reports<sup>101</sup> (MDR) for devices causing death or serious injury are mandatory and must be filed by manufacturers<sup>100</sup> and by user facilities.<sup>101</sup> Table II summarizes MDR reporting requirements for user facilities and manufacturers.

**C2.7 Medical Product Use According to the Label**

Part of the final approval process includes device labeling. Labeling includes all printed material associated with the device, such as actual labels on the device or accessory components, instruction manuals, etc. The Information for Use (IFU) is the most obvious labeling for a medical device, and will contain the specific information on how to use the device. Safety warnings, cautions, along with inclusion and exclusion criteria, together with a summary of clinical trial information are usually provided. Once a device is approved, it may be used in a way that

**Table II. Medical device reporting requirements for user facilities and manufacturers**

<b>Reporter</b>	<b>Event</b>	<b>To Whom</b>	<b>When</b>
User Facility	Deaths	FDA and Manufacturer	Within 10 work days of death
	Reports of serious injuries	Manufacturer (FDA only if manufacturer is unknown)	Within 10 work days of injury
Manufacturer	30-day reports of deaths, serious injuries, and malfunctions	FDA	30 days from becoming aware
	Baseline report to identify and provide basic data on each device that is subject of report	FDA	Within 30-day report when device is reported for the first time
	5-day report on events that require immediate remedial action and other types of events designated by FDA	FDA	Within 5 work days of event

deviates from the label indications, i.e., off-label. The important distinction is if the medical product is used as indicated, medical product liability may belong to the manufacturer. If the medical product is used off-label, the responsibility and liability may shift to the physician and members of the health care team.

### *C2.8 Humanitarian Device Exception (HDE)/ Humanitarian Use Device (HUD)*

One type of specific use is humanitarian use. If the medical device is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States, an applicant can submit a request to FDA's Office of Orphan Products Development for a Humanitarian Use Device (HUD)<sup>102,106</sup> (see 21 CFR 814.102-106 and subpart H).<sup>107</sup> Important items to include in the request are: a statement that the applicant is requesting a HUD designation for a rare disease or condition, a description of the rare disease or condition for which the device is to be used, a description of the device including documentation, with appended authoritative references demonstrating that the device is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year. Once the device has been approved with a HUD designation, an application for a Humanitarian Device Exemption (HDE) can be made to market the device. The HDE application is similar to a PMA application, but exempt from the effectiveness requirements of a PMA.

One of the criteria that must be satisfied in order for a device to receive marketing approval as a HUD device is that no comparable device, other than another HUD approved under the HDE regulation or a device being studied under an approved IDE, is available to treat or diagnose the disease or condition. Thus, FDA may still approve an HDE even if a comparable device is available under an HDE or an IDE. However, once a device with the same intended use as the HUD is approved through either the PMA or 510(k) or process, an HDE cannot be granted for the HUD device. If a device is approved through the PMA process or cleared through the 510(k) process and the labeled indication for the PMA/510(k) is the same as that for the HUD or includes the indication as that for the HUD, FDA may need to rescind the HDE. Thus, once a comparable device with demonstrated safety and effectiveness is available to treat or diagnosis the disease or condition, there would no longer be a need for the HUD and the agency may rescind the HDE.

### *C2.9 Practice of Medicine*

As noted above, using an approved medical product for indications not included in the labeling is allowed under the practice of medicine when used by a qualified licensed healing arts practitioner, but is considered off-label use. When a medical device is being used to treat a patient in an off-label manner, the medical physicist must assume additional responsibility as part of the clinical team treating that patient. Before treating patients, the medical physicist should consult with other members of the clinical team to understand the intended manner in which the device may be used off-label to treat an individual patient. The medical physicist should then perform a thorough investigation of the physics implications for the proposed off-label treatment conditions before individual patients are treated and inform the other members of the clinical team in writing of any physics concerns in the proposed off-label treatment.

Generally, FDA will not be aware if a device is being used systematically in an off-label manner. However, often competitors will complain to FDA if they learn that a device is systematically being used so. Even when FDA learns that a device is being used systematically off-label, there usually is no direct regulatory impact on the practitioner. If the off-label use is a result of promotion by the manufacturer, a warning letter could be sent to, or other regulatory action taken against the manufacturer. The IRB may consider the situation and decide that the consistent off-label use constitutes a clinical trial, and: (1) have the practitioner file an application for a clinical trial covering the use, and if the device as used in a clinical trial is NSR, approve the study; (2) tell the investigator to terminate the procedure; and/or (3) tell the investigator to get an approved IDE for the use. If the IRB or institution has failed to take adequate action to correct the noncompliance, the FDA Commissioner may disqualify the IRB or patient institution.<sup>108</sup>

## APPENDIX D

### Legislative and Legal Details

#### DI. Clinical Investigations

“Off-label” use of a drug or device is not in and of itself “investigational.” A clinical investigation is specifically defined as “any experiment that involves a test article and one or more human subjects.” 21 CFR 50.3(c). Further, only volunteer patients (research subjects) can have access to the device under investigation, and only through a physician who is the investigator. The process is subject to IRB oversight and a protocol must be established and submitted to the FDA by the manufacturer of the device.

The IDE raises the legal issue of informed consent. In this context, FDA regulations specify the circumstances under which informed consent must be obtained (21 CFR 812), and the general requirements of that consent. In particular the consent must contain (21 CFR 50.25):

1. a statement that the study involves research;
2. a description of any reasonably foreseeable risks;
3. alternatives available to the patient;
4. treatments available for any injuries arising from the research involving more than “minimal” risk;
5. privacy and medical records issues;
6. compensation; and
7. a statement that participation is voluntary and may be discontinued without penalty.

In addition, the regulations specify:

1. the informed consent cannot contain “exculpatory language” that would “waive any of the subject’s legal rights;” and
2. before joining the project, the subject must be offered “sufficient opportunity to consider whether or not to participate” under circumstances that “minimize the possibility of coercion or undue influence.” 21 CFR 50.20.

Two exceptions to the informed consent requirement in this context exist:

1. the investigator can forego informed consent in dire, or life-threatening, situations; and
2. there was a limited military exception (21 CFR 50.23), which was used in the 1990 Gulf War.

The provisions of 21 CFR relating to the protection of human subjects is *applicable only to clinical investigations of medical products as defined in the regulations, not to off-label use*. Clinical investigations are defined as IND or IDE trials, and research that, under any FDA regulations, is “intended to be submitted later to, or held for inspection by, the [FDA] as part of

an application or a research or a marketing permit.” The “intent” language of 21 CFR 50.3 (c) “is intended solely as a shorthand way of referring to at least 22 separate categories of information that are now, or in the near future will become, subject to requirements for submission to the agency.”<sup>109</sup>

The medical physicist should not confuse the federal regulatory requirements for informed consent during clinical investigations (e.g., 21 CFR 812) when labeling requirements are being developed, with informed consent requirements typically imposed by state law that apply when physicians treat patients, either following the label or off-label. This is discussed in appendix D, section D3.

## D2. Legislative History and Secondary Sources

The FDA and Congress have stated positions on the meaning of “off-label.” For example:<sup>109</sup>

In 1982, the FDA *Drug Bulletin* informed the medical community that “once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.” The agency went on to state: “unapproved” or more precisely “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature...Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations....FDA Drug Bulletin 4-5 (1982).

FDA statements since that publication affirm this position.<sup>110,111</sup> In 1982, the agency issued a policy statement on the “Use of Approved Drugs for Unlabeled Indications” in the FDA Drug Bulletin. That statement reads, in pertinent part:

The FDCA does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.

*The FDCA provides FDA with explicit regulatory authority over the use of devices* [emphasis added]. The agency’s implementation has been the same, however, because both the statute and the agency’s regulations provide exemptions for the use of devices when a part of the practice of medicine. Letter to Hon. Joseph Barton, *id.* [More recently, an FDA Commissioner testified the history of the FDC Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Thus, once a product is approved for marketing for a specific use, FDA generally does not regulate how, or for what uses, physicians prescribe [it]. A licensed physician may prescribe a drug for other uses, or in treatments, regiments, or patient populations, that are not listed in the FDA-approved labeling.]<sup>112,113</sup>

The suggestion in the above letter that FDA had power to interfere with the off-label use of devices prompted Congress to enact Section 214 of the *Food and Drug Administration Amendment Act* of 1997 (FDAMA), which explicitly prohibits FDA intrusion into medical practice with respect to off-label use of a device or drug. The FDAMA amends the Act to state that

“[n]othing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health-care-practitioner-patient relationship.”<sup>114</sup>

### D3. Liability Theories

There are two broad categories of professional liability cases in medicine

1. Informed Consent
2. Professional Negligence

Let us consider the informed consent category of litigation first. With respect to physicists, the general rule is that there is no duty for the physicist to obtain the informed consent of the patient in any respect. That duty is uniformly held to be the responsibility of the treating physician. This stems in part from the fact that there is no contractual or other relationship between the physicist and the patient. The physicist is either a member of the staff of the hospital, or is an independent contractor retained by the hospital or the physician group. No patient hired the physicist.<sup>115</sup>

The duty to advise the patient is codified in most states. For example, in the Wisconsin case, Wis. Stat., Sec. 448.30 provides in relevant part:<sup>116</sup>

Any physician who treats a patient shall inform the patient about the availability of all alternate, viable medical modes of treatment and about the benefits and risks of these treatments. The physician’s duty to inform the patient under this section does not require disclosure of:

1. information beyond what a reasonably well-qualified physician in a similar medical classification would know,
2. detailed technical information that in all probability a patient would not understand,
3. risks apparent or known to the patient,
4. extremely remote possibilities that might falsely or detrimentally alarm the patient,
5. information in emergencies where failure to provide treatment would be more harmful to the patient than treatment, and
6. information in cases where the patient is incapable of consenting.

Notice that this statute refers to the physician. It does not say hospital, it does not say nurse, it does not say physicist—it says physician. Thus, the informed consent category of litigation is outside the realm of responsibility for the physicist.

Next consider the category of cases under the heading of professional negligence. These turn on the standard rules of medical malpractice litigation. Thus, the introduction of the off-label description introduces no new law; the standard rules of medical malpractice litigation are applicable as far as litigation is concerned.

#### **D4. Principal/Agent or Employer/Employee**

The legal status of the physicist is generally the same as a nurse or anyone else on the medical support staff. If they are an employee of the hospital or a physician group, it is the employer who is ultimately held accountable under the doctrine of *respondeat superior*, which means the employer is responsible for the acts of the employee so long as the acts of the employee or the agent were **within the scope of the employment**. “Scope” is the important word in this context.

#### **D5. Independent Contractors and Indemnity Clauses**

Solo or physics group practices introduce a slight variation in the liability analysis. Theoretically, a physicist could be held directly responsible for professional negligence in this context, and could be held responsible indirectly through the operation of an indemnity clause agreed to in the contract indicating that the physicist (or physics group) agrees to reimburse the physician or hospital for their errors (if such a clause was included in the contractual agreement between the physicist/group and the employing entity whether it was a physician or hospital).

#### **D6. Common Law Theory of Negligence – Analysis**

It is possible that during litigation, a plaintiff attorney may argue that a medical physicist is liable based on negligence. One conceptual illustration of this legal theory may be useful to a medical physicist considering his/her actions involving both on-label and off-label practice. For a medical physicist to be liable under common law negligence, the following elements (although not listed exhaustively and may vary by jurisdictions) may be evaluated:

- a. Duty – one must normally use due care when engaging in any activity which creates a risk of harm to others;
- b. Standard of Care – the determination of whether the medical physicist created an un-reasonable risk of harm depends on the standard of care imposed;
- c. Breach – a factual determination as to whether the medical physicist’s conduct failed to comply with the relevant standard of care;
- d. Cause-in-fact – the injured patient must show that the medical physicist’s conduct was the cause-in-fact of the patient’s injury;
- e. Proximate Cause – there may be a policy consideration limiting the medical physicist’s liability for unforeseeable injury; and
- f. Damage – the injured patient would be entitled to receive compensatory damages for injuries caused by the medical physicist’s negligent conduct.

In a particular case, the determination of negligence and liability would be governed by applicable state or federal laws. However, a medical physicist practicing in an off-label environment could contemplate, for example:

1. Item a above introduces Duty, and section 1 (Introduction) and section 6 (Medical Physicist’s Responsibilities and Dosimetry Issues for Off-Label Use) of this report identify additional responsibilities of the medical physicist (when the patient is

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treated with an approved device which is used off-label), which, if not met, could involve an element of liability analysis.

2. Item b above involves a standard of care and section 7 (Case Studies) may provide potential illustrations of the standard of care for a medical physicist in off-label environments. Section 7 provides guidance on the types of material the medical physicist should consider when told how the device will be used off-label for treatment of an individual patient; however, note that the material in this section is not all inclusive.
3. Item e above involves unforeseeable injury and item 2 in the list of general requirements by FDA regulation on informed consent (21 CFR 50.25 described above in D1) specify “a description of any reasonably foreseeable risks.”

## APPENDIX E

### Reimbursement

The following information is extracted from the Centers for Medicare and Medicaid Services (CMS) website.<sup>117</sup>

#### E1. Coverage of Medical Devices

Medicare may cover certain FDA-approved and IRB-approved investigational devices and services incident to, provided the investigational device meets the following conditions:

- a. Appears on the listing of devices eligible for coverage/payment on CMS' master file of IDE devices;
- b. Is reasonable and necessary for the individual patient;
- c. The device or services associated with the use of a device were provided to the beneficiary within the start and end dates contained in the master file; and
- d. There is no national coverage policy that would otherwise prohibit Medicare coverage.

Medicare may cover services for devices that meet the following conditions:

- a. Devices approved by the FDA through the PMA process;
- b. Devices cleared by the FDA through the 510(k) process;
- c. FDA-approved IDE Category B devices; and
- d. Hospital IRB-approved IDE devices. As of 1 November 1995, Medicare may cover these devices under certain conditions. They have to appear on the listing of devices eligible for coverage/payment on CMS' master file of IDE devices. The services are reasonable and necessary for the patient. They were provided within the start and end dates contained in the master file and there is no national coverage policy that would otherwise prohibit Medicare coverage.

#### E2. FDA Approval IDE Coverage

Each device granted an IDE is assigned a special identifier number by the FDA. Under the FDCA, devices are categorized into three classes. In order to assist CMS in determining Medicare coverage, the FDA will place all approved IDEs in one of two categories:

1. Category A: innovative devices from Class III. These are in general experimental investigational devices.
2. Category B: non-experimental and/or investigational devices from Classes I and II. In addition, some devices from Class III might be included in this category. This is only valid for those devices where the underlying questions of their safety and effectiveness have been resolved.

The CMS does not cover Category A devices under Medicare because they do not satisfy the statutory requirement that Medicare pay for devices determined to be reasonable and necessary. The CMS may cover Category B devices if they are considered reasonable and necessary and if all other applicable Medicare coverage requirements are met. When in doubt, one might refer to the *Medicare Benefit Policy Manual*, Chapter 16, “General Exclusions from Coverage,” Sec. 180 -“Services related to and required as a result of services which are not covered under Medicare.”<sup>118</sup>

### **E3. IDE Reimbursement and Coverage Requirements**

For claims processing and a coverage determination, it is the responsibility of the provider participating in the clinical trial to furnish all necessary information concerning the device, the clinical trial, and participating Medicare beneficiaries that the contractor deems necessary. Medicare contractors are responsible for making the coverage determinations on all FDA-approved Category B devices. Coverage decisions should be made for an FDA-approved IDE, as they currently are made for FDA-approved devices, i.e., the contractor shall apply Medicare’s usual criteria and procedures for making coverage decisions (refer to the CMS Medicare Coverage web page at <http://www.cms.gov/manuals/Downloads/bp102c14.pdf>). The following criteria must also be applied when making coverage determination on FDA-approved IDE Category B devices:

- The device must be used within the context of the FDA-approved clinical trial;
- The device must be used according to the clinical trial’s approved patient protocols;
- There may be an established national policy as contained in existing manual instructions, e.g., National Coverage Determinations Manual instructions, etc.;
- In the absence of national policy, there may be a local policy for similar FDA-approved devices;
- There may be Policy/Position papers or recommendations made by pertinent national and/or local specialty societies.

In addition, contractors should consider whether the device is:

- Medically necessary for the particular patient and whether the amount, duration, and frequency of use or application of the service are medically appropriate; and
- Furnished in a setting appropriate to the patient’s medical needs and condition.

Payment for a Category B IDE device or an IRB-approved device (provided to a non-hospital patient) and the related services may not exceed what Medicare would have paid for a comparable approved device and related services.

### **E4. Hospital IRB-Approved IDE Devices**

Clinical trials for NSR devices (devices which do not require an FDA-approved IDE) are the responsibility of the hospital IRB. While these devices do not require an FDA-approved IDE, many of the FDA-approved IDE requirements apply to these NSR (e.g., they may not be legally

marketed). Medicare contractors are responsible for making the coverage determinations on NSR devices that are the responsibility of the hospital's IRB. Where appropriate, contractors should apply the same coverage criteria to these devices as is applied to FDA-approved IDE Category B devices.

**E5. Payment for IDE Category B Devices**

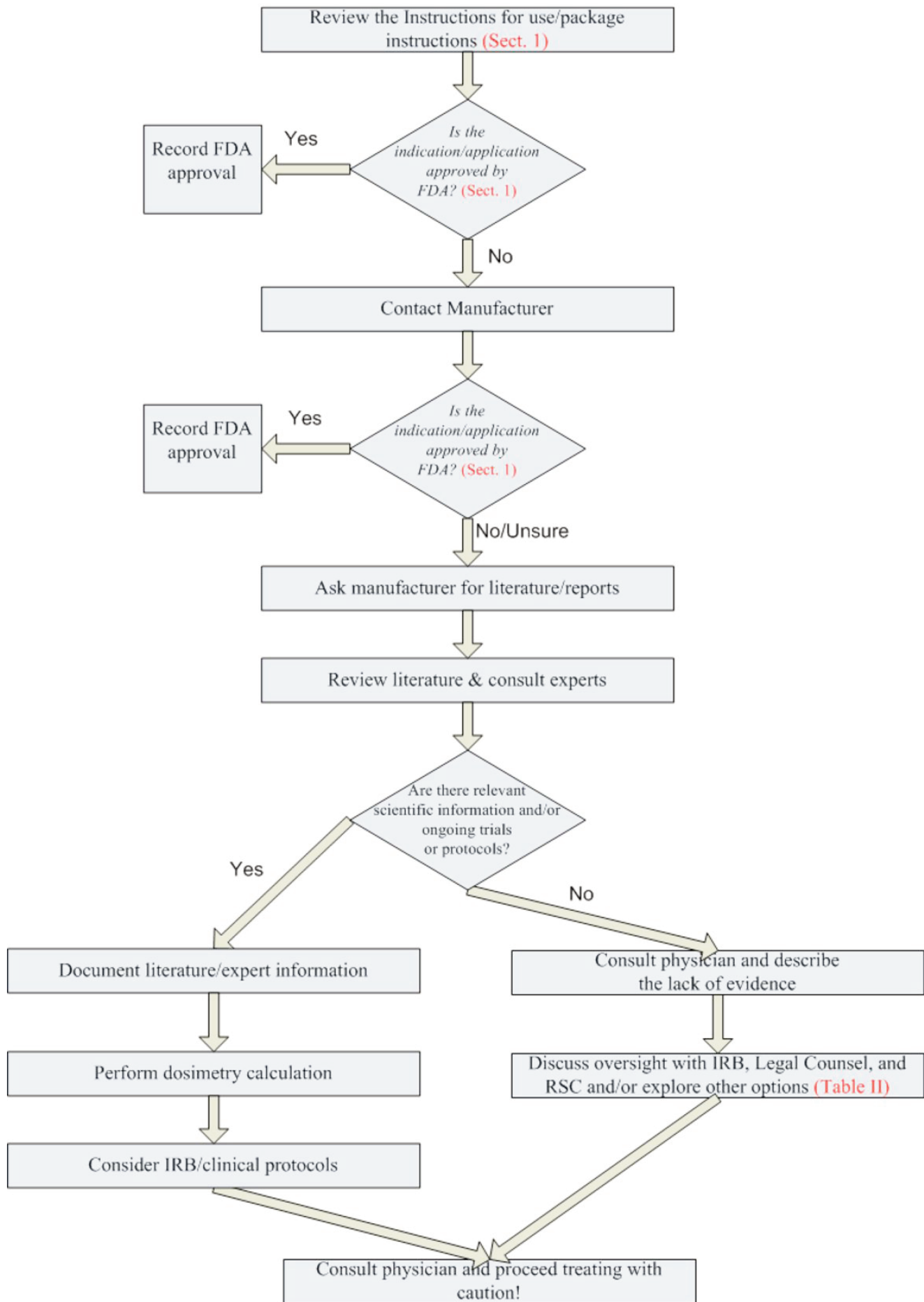
Payment for a Category B IDE device or an IRB-approved device (provided to a non-hospital patient) and the related services may not exceed what Medicare would have paid for a comparable approved device and related services.

## APPENDIX F

### Decision Tree to Assist Physicists in “Off-Label Use” Situations

The following flowchart (Figure 1) illustrates the recommended path to proceed with off-label use for medical devices. It assumes that an individual patient is to be treated in a specific manner that is not included in the device labeling.

The process outlined in this flowchart was implemented and documented for the case of IVBT off-label use for treatment of saphenous vein grafts (SVGs).<sup>72,73</sup> At the time, there was scientific evidence and peer-review publications warranting IVBT treatment of SVGs, but the indication for use was limited to in-stent restenosis. The manufacturer was contacted to confirm these observations, and to obtain additional literature for this off-label use. There were no ongoing trials or clinical protocols available, so the institution decided to pursue in-house review and approval of IVBT for SVG. The local IRB and Legal Counsel were approached, presented the relevant literature, and decided that it could be considered an off-label standard-of-care need. The local Radiation Safety Committee (RSC) was similarly approached, and required that a standardized protocol and custom consent form be prepared. The institution was located in an Agreement State, and a letter was sent to the Radiation Control Program at the State Department of Public Health informing them of the RSC approval and course of action. In summary, the efforts needed to treat patients off-label in a legal, open, and diligent manner were not burdensome. This case study applying the flowchart (Figure 1) of this appendix to IVBT SVGs should be studied. However, each institution has unique requirements for their IRB, Legal Counsel, and RSC oversight, with specific state or NRC regulatory purview.



**Figure 1.** Flowchart of recommended pathway to address off-label uses of medical devices.

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- 109 Beck, supra n. 4 at p. 85 [The legal and ethical distinctions between “research” and “therapy” made in the *Belmont Report* were recognized by FDA when it promulgated Title 21 of the *Code of Federal Regulations* part 50. See 44 *Federal Register* 47,713, 47,716 (Aug. 14, 1979) (referencing *Belmont Report* and other Commission reports).
- 110 Beck, supra n. 4.
- 111 59 *Federal Register* at 59,821. Accord, e.g., 52 *Federal Register* 8798,3308 (Mar. 19, 1987) (reaffirming legality of off-label use); 48 *Federal Register* 26,720, 26,733 (June 9, 1983); 40 *Federal Register* 15,392, 15,393-394 (Apr. 7, 1975); 37 *Federal Register* 16,503, 16,503-4 (Aug. 15, 1972) (“[o]nce [an approved] new drug is in a local pharmacy. . .the physician may, Food and Drug Administration Compliance Program Guidance Manual No. 7382,900 pt. 1 at 7 (1992) (“physicians may use devices for off-label uses...this is considered within the practice of medicine”). “The FDCA does not reference the practice of medicine and FDA does not view its mission to include regulation of the practice of medicine. FDA’s responsibility is the market introduction of new medical products for particular uses...[I]n 1982 the agency issued a policy statement on the “Use of Approved Drugs for Unlabeled Indications,” in the FDA Drug Bulletin, which stated that the FD&C Act does not limit the manner in which a physician may use an approved drug in his or her practice. The Medical Device Amendments (MDA) to the Act give FDA authority to regulated the unapproved use of medical devices. The agency’s actions, however, have been the same across product lines because both the statute and the agency’s regulations provide for specific exemptions from the Act when the use of a device is part of the practice of medicine. [Attachment to letter from FDA to Hon. Joseph Barton, Chairman, Subcomm. On Oversight and Investigation, House Committee on Commerce (Apr. 14, 1995)(citations omitted).] In this same statement, FDA also stated that it does not regulate off-label use.
- 112 Michael Friedman, Deputy Commissioner for Operations, FDA, Prepared Statement Before Subcommittee on Human Resources and Intergovernmental Relations of the House Comm. on Government Reform and Oversight (Sep. 12, 1996).
- 113 William B. Schultz, Deputy Commander for Policy, FDA, Prepared Statement before Senate Comm. on Labor and Human Resources, S. H. 104-445 at 81 (Feb. 22, 1996).
- 114 Pub. L. No. 105-115, Sec. 214, 111 Stat. at 2348 (codified at 21 U.S.C. Section 396 (FDCA Section 906)) (1997).
- 115 *Giese v. Stice*, 567 N.W.2d 156 (Neb. 1997); *Davis v. Hoffman*, 972 F. Supp. 308 (D.C. Pa. 1997); *Stover v. Surgeons*, 635 A.2d 1047 ( Pa. Super. Ct. 1993); *Mathias v. St. Catherine’s Hospital Inc.*, 569 N.W.2d 330 (Wis. 1997).
- 116 Wisconsin Statute 448.30 – Information on alternate modes of treatment.
- 117 <http://www.cms.hhs.gov/manuals/Downloads/bp102c14.pdf> (last accessed 11 May 2010).
- 118 *Medicare Benefit Policy Manual*. Chapter 16, “General Exclusions from Coverage,” Sec.180-“Services related to and required as a result of services which are not covered under Medicare”. <https://www.cms.gov/manuals/Downloads/bp102c16.pdf>.