

Off-label use of medical products in radiation therapy: Summary of the Report of AAPM Task Group No. 121^{a)}

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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 Food and Drug Administration (FDA) approves medical products for use for these specific indications which are part of the medical product's 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 rests with the prescribing physician, medical physicists and others are also 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 the 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 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 recom-

mentations or endorsements of any of the authors or the AAPM. The full report, containing extensive background on off-label use with several appendices, is available on the AAPM website (<http://www.aapm.org/pubs/reports/>). © 2010 American Association of Physicists in Medicine. [DOI: 10.1118/1.3392286]

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I. INTRODUCTION

Medical products, devices, drugs, or biologics must be cleared, approved, or licensed by the 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, and biologics are licensed by FDA's Center for Biologics Evaluation and Research.

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. It allows the FDA to determine whether the device is equivalent to a predicate device which 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 which 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 for a drug, or a Biologics Licensing Agreement for a biologic.

Institutions conducting clinical trials must have the research approved by an institutional review 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. Table I gives special situations under which treatment devices under clinical trial may be used for patients not in that trial.

If the medical product is approved by the FDA for marketing, specific conditions of use are specified in the medical product labeling. Compliance with the specific labeling instructions is an assurance that the medical product is considered by the FDA to be safe and effective for the specific medical indications.

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 U.S., 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

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

Mechanism	Criteria	Timeframe
Emergency Use: 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.	<ul style="list-style-type: none"> • Life-threatening or serious disease or condition; • No alternative; and • No time to obtain FDA approval. 	Emergency use of an unapproved device may occur before an IDE is approved
Compassionate Use: 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.	<ul style="list-style-type: none"> • Serious disease or condition and • No alternative 	Compassionate use can occur during the clinical trial
Treatment Use: 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 suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.	<ul style="list-style-type: none"> • Life-threatening or serious disease; • No alternative; • Controlled clinical trial; and • Sponsor pursuing marketing approval. 	Treatment use can occur during the clinical trial
Continued Use: 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.	<ul style="list-style-type: none"> • Public health need or • Preliminary evidence that the device will be effective and there are no significant safety concerns. 	Continued use occurs after the completion of the clinical trial

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 VI 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.

Appendices referred to in this report can be found in the version on the website of the American Association of Physicists in Medicine (<http://www.aapm.org/pubs/reports/>).

II. 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 which 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 Glasgow¹ related to NRC requirements for intravascular brachytherapy (IVBT) sources. 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 the FDA for marketing, specific 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 the FDA to be safe and effective for the specific medical indications. After FDA approval, certain events must be reported, as given in Table II.

III. 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."² 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.³

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 *et al.*⁴ describe the problem succinctly in their law review article.

Unfortunately, terminology problems persist. It is common parlance to say that a drug or device is FDA "approved"

TABLE II. Medical device reporting requirements for user facilities and manufacturers.

REPORTER	EVENT	TO WHOM	WHEN
User facility	Deaths	FDA and manufacturer	Within ten working days of death
Manufacturer	Reports of serious injuries	Manufacturer (FDA only if manufacturer is unknown)	Within ten working days of injury
	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
	Five-day report on events that require immediate remedial action and other types of events designated by FDA	FDA	Within five work days of event

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 the FDA that an off-label use is actually too unsafe or too risky to appear on the 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.”⁵ A recent notable example of a court falling into precisely this error is *Proctor v. Davis*,⁶ in which the court repeatedly refers to off-label use as “unauthorized” by the 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.⁷

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.⁸ The Legislative History section of Appendix D of the full report 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 labeling 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. The Appendices to this report explore different aspects of the investigational use issue more fully.

III.A. Liability analysis

The discussion above demonstrates that off-label use of medical devices is an accepted part of the practice of medicine (Fig. 1). 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 Ref. 86.

III.B. 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

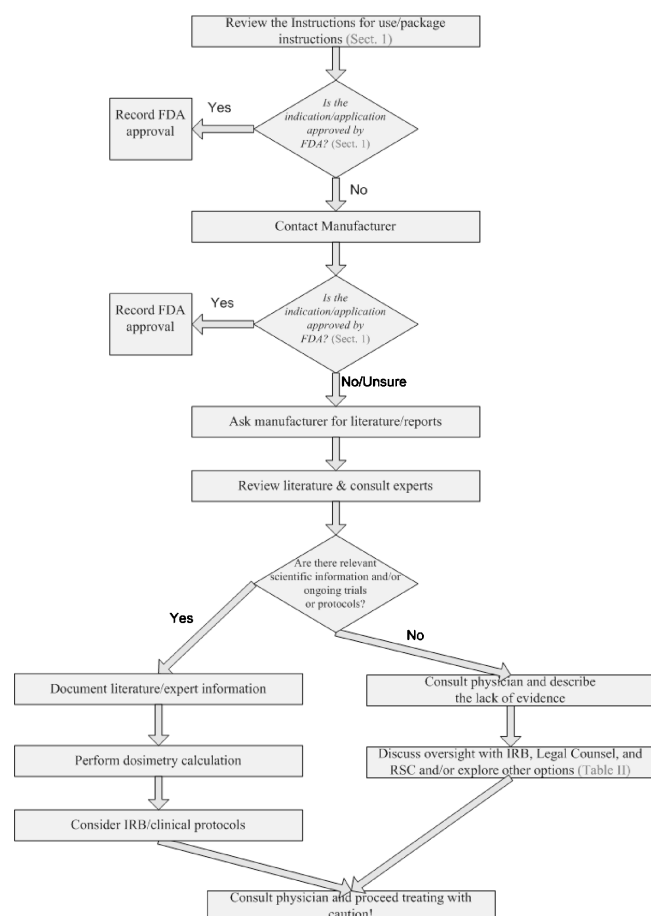


FIG. 1. Flowchart of recommended pathway to address off-label uses of medical devices.

example, Spivak⁹ identifies ongoing DOJ efforts in 2008, investigating and prosecuting cases of illegal off-label marketing. He indicates that according to published reports, there are upward 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 nonpromotional, such as support for medical education and responses to unsolicited requests for information. Spivak⁹ also indicates that not only distribution of drugs is of interest to DOJ, but also devices including software.

In November 2007, the Department of Health and Human Services and the DOJ published “Fraud and Abuse Control Program Annual Report for FY 2006.” 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.¹⁰ 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.

IV. 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.

Experts in the medical field may report on the off-label use of a drug or device through publications, conferences, and other professional forums. Although many medical societies require the presenters to declare 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.

IV.A. Guidance to industry regarding reprint practices

If a physician or healthcare 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^{11,12} in order to provide the current views of the agency. This guidance recognizes that truthful and nonmisleading information from journal articles and reference publications concerning off-label usage can be of benefit to the public health when appropriately distributed to healthcare 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.

IV.B. 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 the 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.

A 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 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, the debate ensues as to the obligation of the manufacturer to undergo the expense and manpower required to conduct the necessary clinical trials and 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."¹³ 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.¹⁴

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.¹⁵ Although the manufacturer can compile the published off-label use of a product and provide that to the 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,¹¹ the FDA does specifically encourage the manufacturer to seek approvals for new uses of approved products.

V. BILLING AND REIMBURSEMENT ISSUES

Reimbursement can be approved for Medicare and Medicaid patients, as well as by third party insurance carriers, for indications which have not been approved by the 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 of the full report for more details on reimbursement.

VI. 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 ⁸⁹SrCl₂ 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 BetaCath source to treat vessel diameters larger than those specified in the labeling. Several problems could be encountered. First could be the 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 (Fig. 1). 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 undesirable results. When desirable results are achieved, it usually occurs when the usage of the device has been con-

sidered 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 undesirable 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 BetaCath 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 region. 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 on undesirable 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).

VII. 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 the 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.

VII.A. Intravascular brachytherapy

VII.A.1. Background

To treat individual patients, IVBT devices were frequently used off-label (see Sec. VII A 2 for more information on their labeling). The first medical products to show significant results in a clinical trial for the reduction in in-stent restenosis following balloon angioplasty were intravascular brachytherapy 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^{16,17} and without^{18–22} interseed spacing), wires,^{23–37} radioactive stents,^{38–40} radioactive liquid filled balloons,^{41–43} radioactive gas filled balloons,⁴⁴ and balloons impregnated with radioactivity.^{45,46} In addition there were peripheral vascular trials⁴⁷ using a HDR ¹⁹²Ir remote afterloading system and external beam therapy for patients with A-V shunts.⁴⁸ 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 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 to, and had the same intended use as, a legally marketed preamendment 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, i.e., a FDA-approved IDE was needed to gather clinical data. Thus, for IVBT devices, a PMA was needed before the product could be legally marketed.

VII.A.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 nonclinical data gathered during the IDE study and submitted in the PMA.

The instructions for use (IFUs) 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.^{49–51}

VII.A.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 noncentered 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 pull-back. In addition to the references cited above, dosimetry from IVBT sources is discussed in the following articles.^{52–63}

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,⁶⁴ effect of plaque on dose rate,^{65,66} effect of contrast media on dose rate,^{67,68} effect of vessel curvature or source movement,⁶⁹ treating peripheral vessels,⁷⁰ treating SVG,^{71,72} dosimetry based on IVUS,⁷³ source pull-back during treatment,^{74–77} use of radiation treatment planning software,⁷⁸ use of well chambers to calibrate sources,^{79,80} and quality management for IVBT.⁸¹

VII.B. Radiolabeled microsphere brachytherapy

Microspheres labeled with ^{90}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) makes TheraSpheres, glass spheres 10–30 μm in diameter with an average ^{90}Y labeling of 2.5 kBq per sphere. TheraSpheres were approved via a Humanitarian Device Exception H980006.⁸² 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."⁸² The other manufacturer, SIRTex, markets resin spheres called SIRSpheres. SIRSpheres are a little larger, ranging from 20 to 40 μm 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).⁸³ The indication for use for these spheres is "... for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic 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 backward (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 diseases 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 document⁸⁴ 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) "Preadministration: 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 postprocedural 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 postadministration entries into the written directive are not an amendment to the written directive; rather, these entries complete the written directive."

VII.B.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 products in place to deliver the dose without filling the capillary bed prematurely. On the other hand, while metastases to the liver may appear as 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:

- Will the injection likely cover the target region adequately without filling the capillary bed prematurely?
- How does the dose as calculated by one system compare to 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.

VII.B.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 microsphere for therapy 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.

VII.B.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.

VIII. SUMMARY

It is important to understand the concept of off-label use of a 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 in the full report 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 Sec. VI. 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 the 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.⁸⁵

^{a)}The opinions expressed herein are those of the authors and are not to be construed as conveying either policies of or an official endorsement or criticism by the U.S. Department of Health and Human Services, the Public Health Service, or the U.S. Food and Drug Administration.

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- aff'd, 643 F.2d 1043, 1052–53 (5th Cir. 1981); *FTC v. Simeon Management Corp.*, 391 F. Supp. 697, 706 (N.D. Cal. 1975), aff'd, 532 F.2d 708 (9th Cir. 1976); *Upjohn Co. v. MacMurdo*, 562 So.2d 680, 683 (Fla. 1990); *Jones v. Petland Orlando Store*, 622 So.2d 1114, 1115 (Fla. Dist. Ct. App. 1993); *Haynes v. Baton Rouge Gen. Hosp.* 298 So.2d 149, 153 (La. Ct. App. 1974), writ denied, 302 So.2d 33 (La. 1974); *Peter Hutt, Regulation of the Practice of Medicine Under the Pure Food & Drug Laws*, 33 Food & Drug Officials Q. Bull. 7–11 (1969).
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- ⁷See, e.g., *Washington Legal Foundation v. Kessler*, 880 F. Supp. 26, 28 n. 1 (D.D.C. 1995). Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." W. Christopher, "Off-label drug prescription: Filling the regulatory vacuum," 48 Food and Drug Law Journal, pp. 247–262 (1993) (footnotes omitted).
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