COMMISSION BRIEFING SLIDES/EXHIBITS

PROPOSED RULE ON PART 35

MEDICAL EVENT DEFINITIONS

JULY 8, 2010

U.S.NRC

United States Nuclear Regulatory Commission

Protecting People and the Environment

Part 35 Reproposed Rule on Medical Event Definitions

R. W. Borchardt

Executive Director for Operations

July 8, 2010

Agenda

- History
- Stakeholder Involvement
- Development of Rule
- Conclusion

History

- 1973 - Proposed Misadministration Rule
- 1980 - Final Misadministration Rule
- 1987-2002 - Three Major Revisions of Part 35

Stakeholder Involvement

- ACMUI
- Medical community
- Other stakeholders

Medical Event Summary

Year	Total ME Reports[1]	# 35.400 Prostate Reports[1]	# of Prostate Patients
2004	35	5	5
2005	41	5	5
2006	33	5	5
2007	40	8	25
2008	31	9[2]	115
2009	46	15[2]	23
Average	38	8	

[1]Approximately 150,000 therapeutic procedures are performed each year, of which less than 50,000 are permanent implant brachytherapy procedures.
[2]8 DVA Permittees reported during one or both years (121 patients - 97 from 1 facility).

Purpose of Rule

- To prevent recurrence;
- To identify potential generic problems; and
- To allow timely decisions on health care

Development of Rule

- **2004 ACMUI Commission Meeting**
  - **Are we communicating the right risk information?**
- **SECY-05-0234**
  - **Recommendation based on input from ACMUI**

Development of Rule (cont'd)

- **SECY-08-0080**
  - **Proposed rule changes most ME criteria from dose- to activity- based**
- **SECY-10-0062**
  - **Adds some new-activity-based criteria**
  - **Retains dose-based criteria**

Conclusion

- Medical event reporting required since 1980
- Protect patient safety without intruding on the practice of medicine
- Stakeholder involvement throughout rule development

Acronyms

- ACMUI - Advisory Committee on Medical Uses of Isotopes
- DVA - Department of Veterans Affairs
- ME - Medical Event
- SECY - Office of the Secretary

U.S.NRC

United States Nuclear Regulatory Commission

Protecting People and the Environment

Briefing on Proposed Rule on Part 35 Medical Events Definitions – Permanent Implant Brachytherapy

July 8, 2010

James Welsh, M.D.

Advisory Committee on the Medical Uses of Isotopes

Introductory Comments

- **A goal: Medical Events should be based on potential clinical significance**
- **This necessitates a careful balance:**
  - **Avoiding overly sensitive clinically-insignificant definitions (which might overburden the system)**
  - **And ensuring that the definition will identify those procedures that are potentially harmful**
- **This is a difficult task and everyone wants to get it right**
- **The Subcommittee believes that the re-proposed rule in its present form would not be successful in this very challenging balancing act**

Medical Events

- **An appropriate definition of a Medical Event is one that reflects the real potential of harm to a patient**

- **"Harm to a patient" can be from:**
  - **Overdosing normal tissues**
  - **Substantially under-dosing the targeted cancer**

- **Again this requires a very careful balancing act between these two parameters when attempting to come up with acceptable definitions of Medical Events**

Inherent Difficulties With an Appropriate Definition for Medical Events for Permanent Implant Brachytherapy

- **Brachytherapy is an art as well as a science**
- **No simple definition of Medical Event adequately covers all potential adverse circumstances**

Challenges

- **In the past ACMUI has not endorsed the concept of an absorbed dose-based criteria**
- **However, the Subcommittee now acknowledges that there may be rare situations in which activity-based criteria may be inadequate**
- **On the other hand, all previously proposed dose-based criteria create new difficulties or face new challenges**

Challenges (and solutions)

- The difficulty posed by post-implant volume change and absorbed dose calculations
- The dose in the following examples will deviate from the Written Directive yet are NOT considered Medical Events – they are "patient-related factors"
  - If a temporary implant is yanked out by a patient
  - If a seed migrates out of place after being properly positioned
  - Stasis reached during a Y-90 microsphere procedure
- The Subcommittee suggests that alterations in dose due to anatomic prostate volume changes also be considered a "patient-factor" and thus excluded from Medical Event definitions

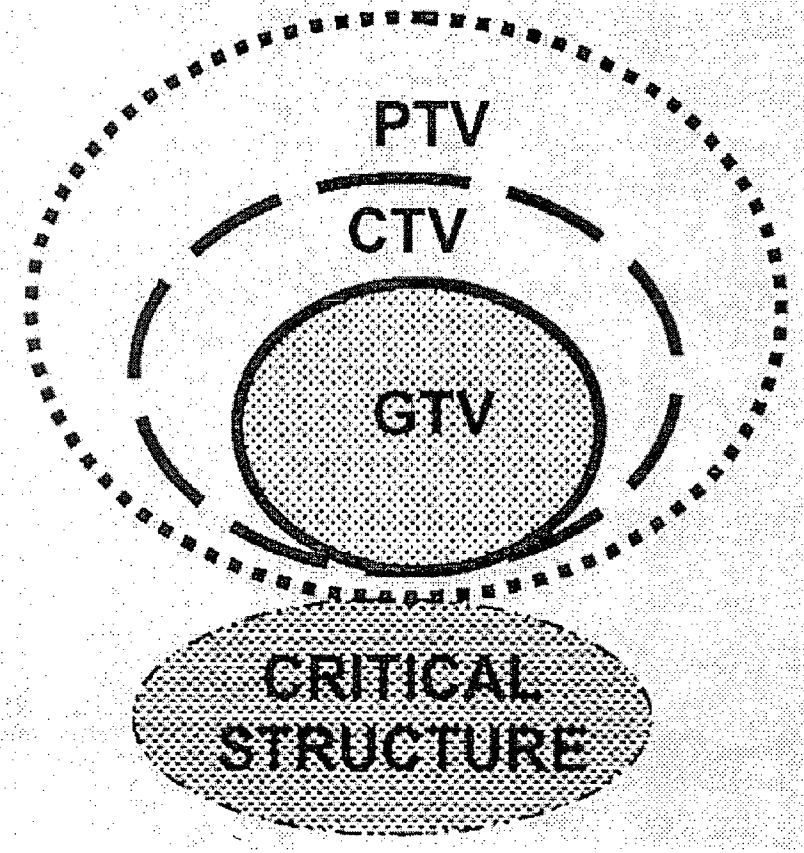
A Proposed Concept

- **If using a dose-based criterion, we suggest introducing the concept of normalization to the initial volume *V(init)* on which the authorized user has created the plan**
- **There can be differences in volumes calculated**
- **In addition to addressing the concern about anatomic post-implant volume changes that affect dose calculations, V(init) also addresses the problems faced by the above non-anatomic volume differences**

A Proposed Concept

- **The V(init) concept might be easily implemented**
  - **Pre-implant prostate volume is known for all implants**
  - **It does not require additional effort**

- **To properly address Medical Events in permanent implant brachytherapy we recommend that modern terminology be used rather than "treatment site"**



Volume abbreviations:
GTV = gross tumor volume
CTV = clinical target volume
PTV = planning target

Post-implant Dosimetry

- **The Subcommittee is divided about the insistence on post-implant dosimetry**

Final Thoughts on Dose-based Criteria

- Returning to the original concept of a Medical Event as something that could be of "harm"
  - Perhaps a solution would be to shift the emphasis, focusing more (or equally) on dose to normal tissues
  - This would adequately address the goal of identifying potential harm to a patient
  - Overdoses to normal tissues (i.e. an absorbed dose that exceeds normal tissue tolerances) are potentially harmful
- ACMUI also has a suggestion that would address "harm" due to under-dosing the target and not curing the patient

Conclusions

- **The ACMUI Permanent Implant Subcommittee is opposed to certain aspects of the re-proposed rule and urges the Commission NOT to publish it in its present form**

- **The matter is complicated and will have a huge impact on the regulated community**

Conclusions (continued)

- **Therefore, it is imperative that the ultimate version be correct (the re-proposed rule fails in too many aspects)**

- **We recommend that NRC seek stakeholder input during any revision**

- **If NRC desires a dose-based criterion, the Subcommittee is prepared to offer an understandable, unambiguously measurable and carefully considered solution based on all of the above**

Medical Events Definitions Permanent Implant Brachytherapy

July 8, 2010

Darice G. Bailey, Texas Dept. of Health Services

Representing the Organization of Agreement States

Comments Made During Regulation Development

August 2008 proposal

Concern: Direction was given to NRC staff to change from a dose based Medical Event definition to an activity based definition without agreement state input or full review of the impacts

Comments Made During Regulation Development

2010 Proposed Regulation

Comment has been adequately addressed.

This rule tightens the dose based variables and includes the addition of activity based variables.

Comments Made During Regulation Development

2010 Proposal

- The basis for the 20% variance in defining a Medical Event (ME) causes concern
- A numeric basis is necessary, but the percentage may need to be adjusted based on results of implementation

Comments Made During Regulation Development

- Support the addition of a deadline for assessing the dose to the patient from the implanted radioactive material
- This time frame is a missing link in the regulation currently being enforced.

Comments Made During Regulation Development

Support that the absence of a written directive does not, by itself, drive a determination of a Medical Event

Radiation Safety

Regulators walk a fine line, in rule development, between writing an enforceable rule and treading on the practice of medicine

OAS' focus is on radiation safety. We do not ever want to limit patient care and treatment in our efforts to enforce regulations.

Compatibility

The states agree with the proposed compatibility levels for regulation changes, but reserve concern over how adoption of essential objectives will be determined in reviewing individual state's rules.

Department of Veterans Affairs
PATIENT CARE SERVICES

NRC Briefing on Proposed Rule on Part 35 Medical Events Definition-Permanent Implant Brachytherapy

July 8th, 2010

Michael Hagan, M.D., Ph.D.
National Director Radiation Oncology
Patient Care Services
Veterans Health Administration

Department of Veterans Affairs
PATIENT CARE SERVICES

35.3045 Report and notification of a medical event.

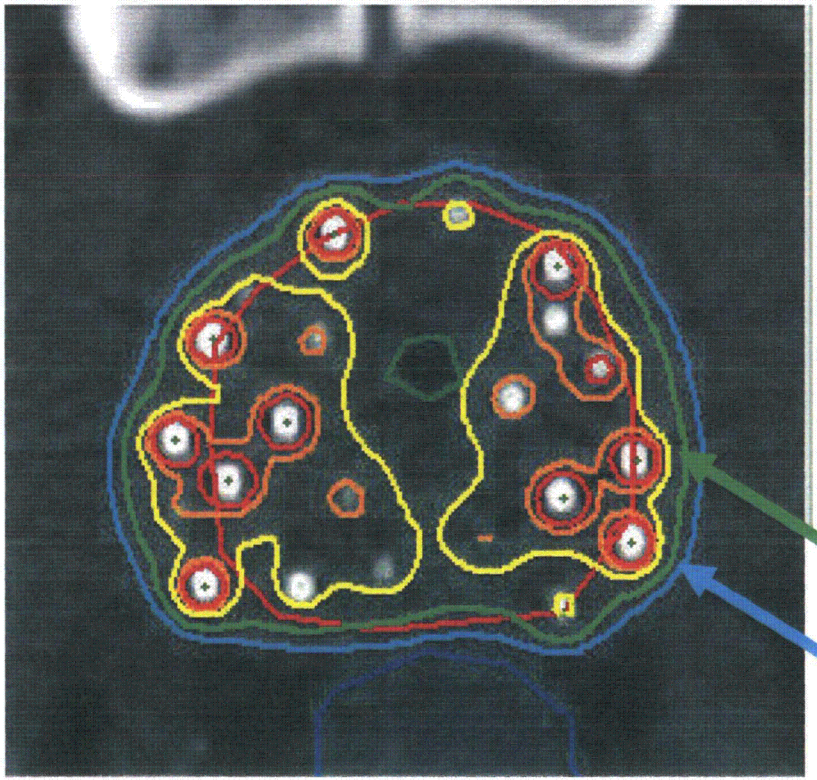
- a) A licensee shall report any event …

(i) … dose delivered **differs from the prescribed dose by 20 percent or more**;

(3) A dose… **to an organ or tissue and 50 percent or more of the dose expected from the administration defined in the written directive…**

Department of Veterans Affairs
PATIENT CARE SERVICES

Focusing on small deviations in the peripheral dose overlooks the actual dose distribution



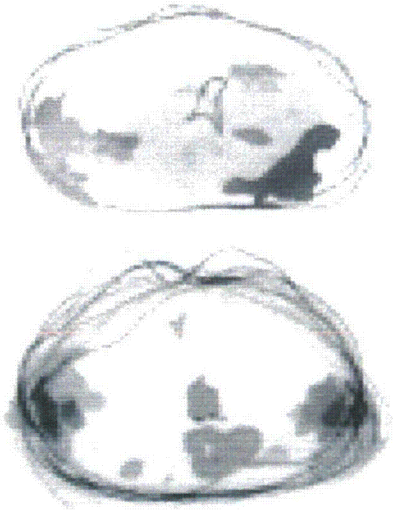
Dose (Gy)	Dose (%)	Color
☑ 362.5	250 %	
☑ 290.0	200 %	
☑ 217.5	150 %	
☑ 145.0	100 %	
☑ 116.0	80 %	

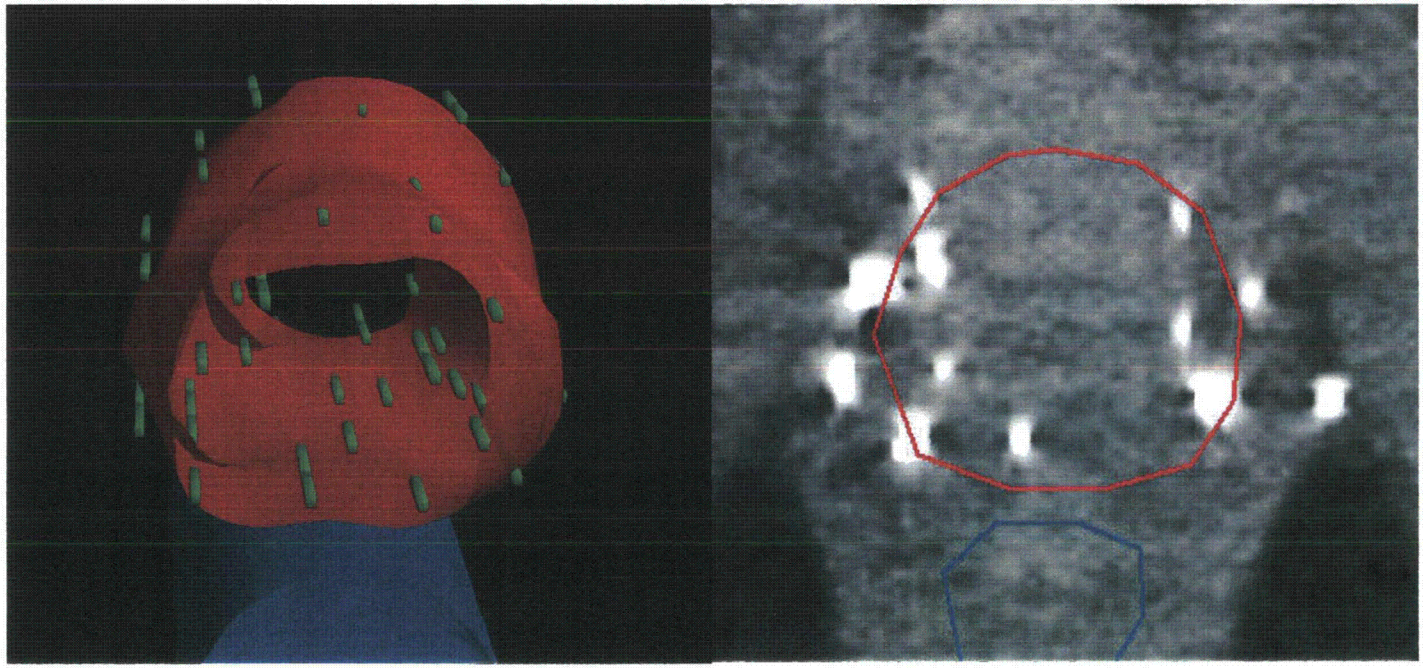
Excellent coverage

Medical event

Department of Veterans Affairs
PATIENT CARE SERVICES

Clinician may design the seed distribution to match the anatomic disposition of tumors





Here, the clinician, aware low-risk patients have a low incidence of disease in the anterior prostate, reduces coverage to lower toxicity

Egawa et al. 2000, JJCO 30: 126.

Department of Veterans Affairs
PATIENT CARE SERVICES

35.2 Definitions.

- *Prescribed dose* means—

(3) For manual brachytherapy, **either the total source strength and exposure time or the total dose**, as documented in the written directive;

Department of Veterans Affairs
PATIENT CARE SERVICES

Conclusions

- For the prostate treatment volume no absorbed dose metric can be determined within the accuracy limits required for regulatory assessment.
- Placement of byproduct material within the treatment site is under the control of the Authorized User.
- Assessment of this placement is sufficient for regulatory compliance.

Clinicians vary seed distribution: Preplan and post-plan confirm the physician's intentions

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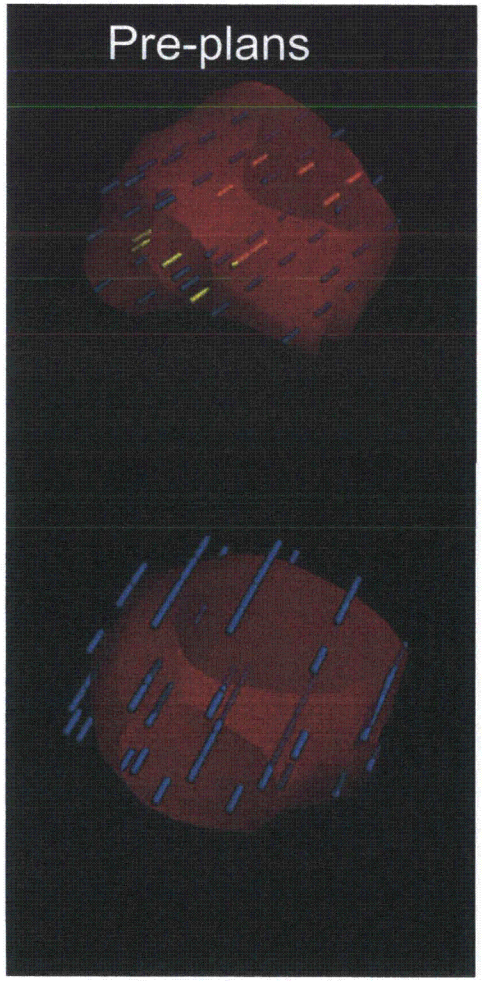
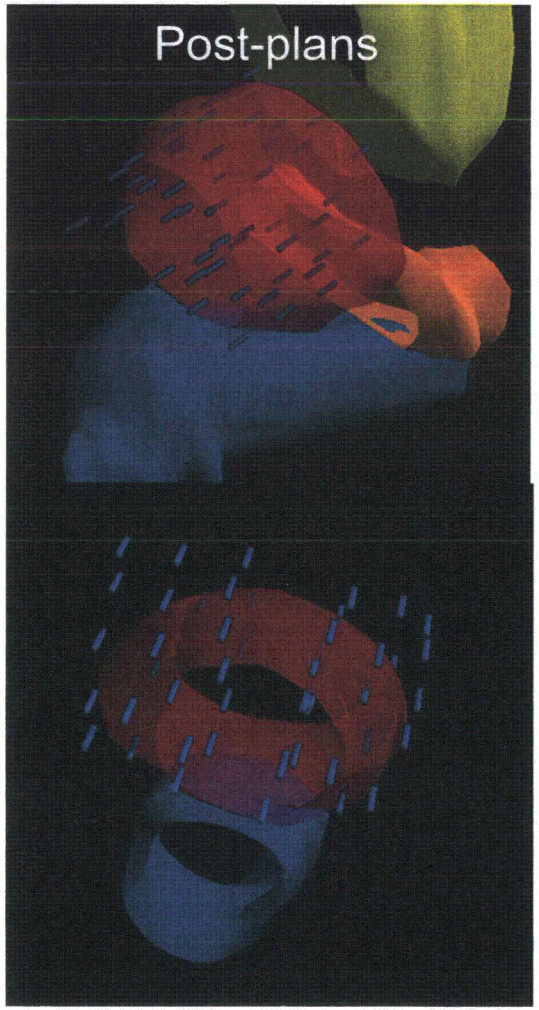


Moderate activity seeds largely within the prostate

Prostate dose varies markedly with the volume

High activity seeds placed outside of the prostate

Prostate dose varies minimally with the volume, but more dose to adjacent tissue



NRC Briefing on Proposed Rule on Part 35 Medical Events Definition-Permanent Implant Brachytherapy

July 8th, 2010

Michael Hagan, M.D., Ph.D.
National Director Radiation Oncology
Patient Care Services
Veterans Health Administration

SLIDE 1

By requiring an absorbed dose metric for the evaluation of the prostate dose from a volume implant, NRC directs the practice of medicine.

It is the purpose of the regulatory evaluation to determine whether the authorized user (AU) has used byproduct material as intended. To accomplish this task, 10CFR35 details requirements involving both a Written Directive and a post-procedure dose evaluation.

By rule, the specific regulatory limit for the prostate target is + or – 20% of the dose prescribed, while other "organs and tissues" are held to less than 150% of their expected doses.

SLIDE 2

A quite natural follow-on from these requirements is the desire to know both the intended radiation absorbed dose and the actual dose resulting from the placement of the regulated material.

Indeed, the Veterans Health Administration's Blue Ribbon Panel recommended the use of routine dose-volume histogram analysis to determine the dose delivered to "other organs and tissues," namely the bladder, rectum and peri-prostatic soft tissues.

This is not the case, however, for the prostate itself. In 2005, the Advisory Committee on the Medical Uses of Isotopes (ACMUI) correctly advised the NRC that for the regulatory evaluation, no absorbed dose metric could be applied to a volume implant, such as a permanent interstitial implant of the prostate.

The explanation for this categorical rejection is four-fold.

1. The absorbed-dose received by the target volume cannot be reasonably determined. It can only be estimated.

2. The authorized user cannot accurately control the absorbed dose during the period when the estimate is obtained.

3. No absorbed-dose measure reflects the physical dose-distribution within the regulatory limits. For example, under a very specific set of circumstances the D90 value could apply to the lower dose limit, but never to the upper limit.

4. During the post-implant dose assessment clinicians vary considerably on their delineations of the target for the prostate treatment site, which markedly alters any measure of absorbed dose.

Specifically, the absorbed dose is a prostate target volume-dependent parameter and this target volume varies substantially during dose delivery. While the median increase in prostate volume due to edema following an interstitial implant has been estimated to be 50%, the range may extend from 0-200%[1-3]. Further, post-implant edema, which varies with the implant technique, resolves with a variable half-life, estimated to be between 4 and 26 days[2]. Consequently, dose measurement on a single day of the volume trajectory provides only a point estimate. How closely this estimate relates to the actual absorbed dose depends upon the residual edema on the day of the estimate, which is not in the AU's control.

SLIDE 3

Notice here the prescription isodose and the isodose which defines a medical event are only 1mm -3mm apart. On this day, this prostate is >50% larger than the morning of the implant. Its radius has expanded by 9mm, over three times the separation between the critical isodose contours.

Finally, focusing on a 20% limit around the minimum peripheral dose (MPD) estimate overlooks inevitable and constantly changing realities.

At any moment, *as is true for the prostate you are seeing*, greater than 50% of the treatment volume may receive 150% of the prescription dose. At the same time a substantial portion of the prostate may receive up to 200% of the prescription. Moreover, practitioners intentionally vary the amount of tissue they want to cover in a given clinical scenario.

SLIDE 4

In the next slide the clinician has decided to reduce coverage of the anterior prostate for a patient with a scant volume of low-risk disease. Yet regulators preferred to evaluate this implant for uniform coverage by the MPD of the entire CT volume.

It follows then that clinical outcome cannot be directly and reliably related to any single measurement of absorbed dose[4-10]. As a result many clinicians are more interested in the source distribution with respect to likely tumor locations for a given patient or presentation of disease, than obtaining a certain MPD to uninvolved regions.

Note that in this slide the seed distribution follows reasonably well the tumor distribution reported for low volume prostate cancer[11].

Requiring practitioners to obtain a specific minimum peripheral absorbed dose for the prostate, the regulator directs medical practice.

Regulators should focus on the original task of determining whether the AU used the byproduct material as he intended, whilst avoiding parameters uniquely within the expertise of the AU. Using available technology, the AU can control with acceptable accuracy the initial anatomic placement of source material. Regulatory limits must themselves be limited by the predictable deployment of the isotope.

The AU is required to verify that more than 80% of the dose was applied to the treatment volume. For these procedures 10CFR35.2 (SLIDE 5) defines dose by source strength and time. Assessing that the sources were delivered where they were intended to be delivered is sufficient for effective regulatory oversight.

That regulation would attempt to fully manage and control the complex matrix of the local biology of the recently implanted prostate has no precedent. Regulatory organizations have neither the experience, nor the appropriate training and credentials for these decisions.

Therefore, on behalf of the entire RO community with our collaborating urology colleagues, we urge the NRC to focus on the appropriate areas of training and skill with which it can continue to be a very effective voice for safe use of therapeutic radioactivity.

Once it can be determined that the placement of source material has followed written procedures including the written directive, how the dose develops from that source placement and how in turn the delivered dose eliminates deposits of disease or produces toxicity is the responsibility of the physician, not the province of the regulator.

SLIDE 6 Conclusions

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AAPM Comments on the Reproposed Rule on Permanent Implant Medical Events

July 08, 2010
Douglas Pfeiffer, MS, DABR
Chair, AAPM Governmental and Regulatory Affairs Committee
(AAPM: American Assoc. of Physicists in Medicine)

General Response

- NRC has addressed the major points of the 2008 AAPM comments
- Reproposed rule attempts to balance the needs of both conventional pre-plan and real time planning (prostate) along with other implant procedures

Training

- AAPM agrees with the requirement for documented training on the requirements of §35.3045
- Suggest that a 2 year interval might be reasonable and sufficient

Written Directives

- AAPM agrees with the establishment of pre-implantation and post-implantation sections of the written directive
- We reinforce the need to be able to revise the WD in the OR, prior to start of administration
- §35.40(c)(2) should specify that the oral revision must be performed prior to the start of the administration to avoid any ambiguity

Written Directives

- Consider the case in which loaded peripheral needles and loose seeds are ordered based on early preplan (month before). Peripheral needles are implanted. Plan is then made for internal seeds
- WD cannot be completed prior to start of procedure in this case
- Pre-implantation WD for real-time dosimetry implants should be based on dose, not activity

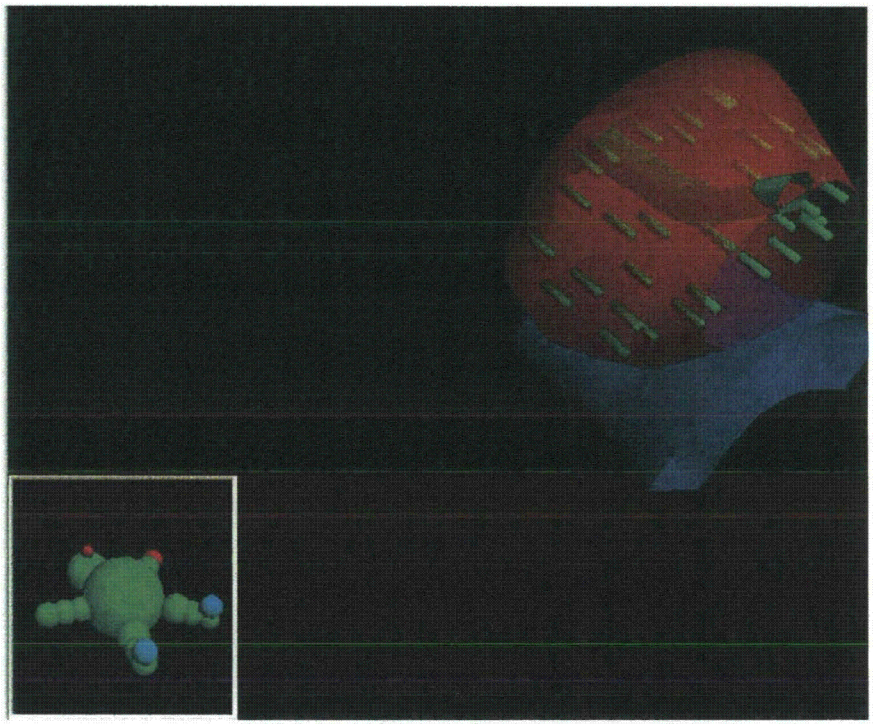
Written Directives - Questions

- Does NRC expect that the WD will contain dose intent for organs at risk, such as rectum, bladder, urethra?
- Are the requirements of §35.41(d) met by the final treatment record in real-time dosimetry implant?

Dose Information

Prostate:

Total Volume:	17.42 cc	
V200%:	4.68 cc	[26.85%]
V150%:	10.03 cc	[57.62%]
V100%:	16.20 cc	[93.04%]
D90%	126.91 Gy	[105.76%]
D50%	191.40 Gy	[159.50%]
D1%:	899.71 Gy	[749.76%]



Urethra:

Total Volume:	0.53 cc	
D90%	73.79 Gy	[61.50%]
D30%	158.05 Gy	[131.71%]
D10%	163.24 Gy	[136.03%]

Rectum:

Total Volume:	5.64 cc	
V100%:	0.00 cc	[0.00%]
D30%	54.66 Gy	[45.55%]

ME Reporting

- AAPM agrees with the modification that the lack of a WD is a ME if other documentation is insufficient to establish if a ME has otherwise occurred

General Comment

- AAPM commends the NRC for the references to "published protocols accepted by nationally recognized professional organizations" (e.g. AAPM Task Group Report 137: Low Energy Brachytherapy Source Dosimetry Work Group Task Group #137) rather than extracting selected text from these documents and placing the text in a regulatory rule, a role for which the documents were not intended.

Concluding Remarks

- AAPM agrees with reproposed rule with minor modification
- AAPM thanks NRC for its consideration of its 2008 comments and those of other groups

July 8, 2010

David P. Houchens, Ph.D.

Treasurer, Board of Directors

Us TOO Mission

- **Communicate timely, personalized, and reliable information**
- **Enable informed choices regarding detection and treatment of prostate cancer.**

Us TOO Chapter Network

- TOTAL - 327
- United States – 300
- International - 27
  - England – 8
  - Canada – 7
  - Scotland – 4
  - Australia, Bahamas, Belgium, India, Netherlands, South Africa, Spain

Us TOO Support Groups

- Peer-to-peer support
- Personal information sharing
- Partners, companions and families
- Educational symposia & workshops

Central Office Support

- Us TOO website
  - Newsletter
  - Resource publications
  - Materials for health fairs
- Patient referrals
- Chapter leader support
- Identity as an international organization.

Online Discussion Groups:
Prostate Pointers

14 moderated bulletin boards

1. **P2P - Physician-to-Patient**
2. **SeedPods – brachytherapy, radioactive seed implants**
3. **PCAI – prostate cancer and intimacy**
4. **The Circle – PCa support, wives and partners**
5. **RP – radical prostatectomy**
6. **EBRT – external beam radiation therapy**
7. **CHB – combined hormonal blockade**
8. **HAH – humor and healing**
9. **IceBalls - cryosurgery**
10. **NewDx – newly diagnosed**
11. **Spirit – spiritual support**
12. **WW – watchful waiting**
13. **PCAN – prostate cancer action network**
14. **Promise – grieving a loss**

Educational Programs

- **Topic-related teleconferences & web-casts**
- **Minority & Underserved Populations**
- **Awareness Program**
- **Companions & Families Program: *Circles of Love***
- **Us TOO University**

Advocacy

- **One Voice Against Cancer (OVAC)**
- **Cancer Leadership Council (CLC)**
- **National Health Council – Voluntary Health Agencies member**
- **Conferences & meeting attendance:**
  AUA, ASCO, NCPC, PCF, etc.

Us TOO Recommendations

- **Early detection decreases deaths and improves quality of life.**
- **Benefits of early detection and treatment outweigh the cost and inconvenience of occasional false positives.**

The Growing Challenge

- **Knowledge is power**
- **230,000 diagnosed each year**
- **in the next 10 years to 300,000 (+40%)**
- **1 in 6 of Baby Boomer men**
- ***6.6 million men at risk***

Areas of concern for patients

- Treatment outcome
- Quality of life
- Knowledge that the doctors they have chosen for treatment have both expertise and experience in their field

"Never doubt that a small group of thoughtful, committed citizens can change the world: indeed, it's the only thing that ever has."

Margaret Mead