World Wide Medical Technologies

CITIZEN PETITION

2005P-0054

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February 18, 2005

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Rm. 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Re: Citizen Petition Urging FDA to Safeguard the Public From Commercial Brachytherapy Kits for the Treatment of Prostate Cancer that Use Non-Absorbable Bone Wax or Non-Absorbable Reformulated "Faux Bone Wax" Needle Plugs

Dear Sir or Madam:

Overwhelming scientific data published in journals from the fields of orthopedic, mastoid, thoracic, cardiac, foot, plastic, ophthalmic, and dental surgery indicates that the migration of bone wax from surgical bone sites into areas of soft tissue within the body can potentially lead to serious complications, including the formation of cancerous tumors. Bone wax is a substance that was developed as a hemostasis agent for use in bone, and, to the best of our knowledge, it has only been cleared by the Food and Drug Administration ("FDA"), as a stand-alone product, to stop bone bleeding locally.[1]

Accordingly, we believe that the recent introduction of commercial brachytherapy kits for the treatment of prostate cancer – *i.e.*, pre-plugged, pre-loaded needles used in brachytherapy

[1] *See, e.g.*, United States Surgical Corporation, 510(k) No. K971680, Oct. 24, 1997 (claiming "substantial equivalence" with Johnson & Johnson's Ethicon™ (preamendment) and Lukens™ Bone Wax (K791405)) (Att. 1); CP Medical, Inc., 510(k) No. K024372, June 19, 2003 (Att. 2).

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treatment – that use off-label non-absorbable bone wax or reformulated "faux bone wax"[2] raises significant safety issues.[3]

Executive Summary

Alarmingly, we believe companies that manufacture the radioactive "seeds" that are used in commercial brachytherapy kits, and the subcontractors who assemble these kits for them, have recently begun to market these commercial kits to hospitals and physicians without giving appropriate consideration to the potential dangers identified in the scientific literature. When used, these kits permanently implant a substantial amount of bone wax or reformulated "faux bone wax" into soft tissue, which according to the literature can potentially cause a myriad of complications, including:

- Sarcomas (*e.g.*, angiosarcomas),
- Chronic inflammation (granulomatis infection),
- Marked foreign body reaction,
- Epistaxis,
- Allergic reactions,
- Sigmoid sinus thrombosis,
- Foreign body venous embolization,

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[2] Reformulated "faux bone wax" refers to a reformulation of bone wax that has been used as needle plugs, and to the best of our knowledge, it is untested. It is our understanding, through independent laboratory testing, that traditional bone wax has been reformulated by adding fibrous substances to raise the product's melting point to make it less sticky and more solid at higher temperatures. *See* Jordi Letter, dated July 14, 2003 (Att. 3). We can only opine that certain manufacturers have developed reformulated "faux bone wax" because bone wax needle plugs proved to be unstable during shipping.

[3] Companies that we believe may sell brachytherapy kits containing bone wax or reformulated "faux bone wax" include Mentor Corp., Best Medical, International Brachytherapy, S.A. ("IBt"), and BEBIG Isotopen-und Medizintechnik GmbH ("BEBIG"). *See* Miscellaneous Promotional Material for Kits Using Bone Wax or "Faux Bone Wax" Plugs (Att. 4).

- Pulmonary complications, due to migration to the lungs, and
- Quadriplegia

Given that approximately 232,090 American men are expected to be diagnosed with prostate cancer in 2005 alone,[4] and that approximately 40,000 of those men will choose to undergo brachytherapy treatment,[5] commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" pose a massive public health threat. The extent of this public health threat, however, cannot yet be known, as it can take years for complications to manifest.

This massive public health threat may be averted, or at least minimized, given that commercial brachytherapy kits that use off-label bone wax or reformulated "faux bone wax" needle plugs, to date, have likely only impacted a few thousand patients. Accordingly, if the FDA acts quickly to remove the products from the market, at least until the kits can be proven to be safe, substantial adverse health events may be avoided.

Therefore, this petition is respectfully submitted pursuant to 21 C.F.R. § 10.30,[6] to urge that the Commissioner of the FDA: (1) ban the use of commercial brachytherapy kits that use non-absorbable bone wax or reformulated "faux bone wax" needle plugs, under Section 516(a)(1) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), because they present an "unreasonable and substantial risk of illness or injury,"[7] or (2) at minimum, require all manufacturers of such commercial brachytherapy kits to obtain FDA approval of a premarket approval application ("PMA") prior to commercial distribution, which would force manufacturers to affirmatively prove that such kits are safe and efficacious.[8] Regardless of whether FDA decides to ban bone wax or reformulated "faux bone wax" kits, or require PMAs, FDA should also rescind any

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[4] *See, e.g.*, American Cancer Society Website (estimating that 232,090 American men will be diagnosed with prostate cancer in 2005), http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_men_get_prostate_cancer_36.asp?sitearea= (Att. 5).

[5] Louis Potters, M.D., *Permanent Prostate Brachytherapy in Patients with Clinically Localized Prostate Cancer*, Men's Health and Cancer, malecare, http://www.malecare.org/new_page_93.htm (the 40,000 figure is based on a 2001 estimate) (Att. 6).

[6] 21 C.F.R. § 10.30 (2004).

[7] 21 U.S.C. § 360f(a)(1) (Supp. 2004). As explained herein, we do not believe that the unreasonable and substantial risk of illness or injury could be corrected or eliminated by labeling modifications.

[8] Notably, this Citizen Petition only addresses commercial brachytherapy kits and is not intended to affect brachytherapy systems assembled by medical professionals prior to performing brachytherapy surgery.

current "substantial equivalence" orders for such kits and remove from the market any brachytherapy kits currently marketed in the absence of 510(k) clearance or approval.

The above actions would have no adverse impact on prostate cancer patients as brachytherapy kits containing bioabsorbable plugs or needles designed to obviate the use of plugs altogether have already been cleared by the agency and are readily available.

A. Background and Overview

Brachytherapy is an out-patient cancer treatment that is an accepted alternative to general surgery. It involves placing a pattern of radioactive sources into the body to destroy cancer cells with low dose radiation. These radioactive sources, or "seeds," are placed into the body using multiple hollow needles. These needles act as holders and carriers of these seeds until the needles are inserted into predetermined areas of the body.

Usually, between 15 and 60 needles are used in each procedure. Typically, in a hospital, a medical physicist prepares the needles and loads the seed sources and spacers into each needle prior to the procedure. The delivery end of the needle is closed for the first 2-5 mm with bone wax[9] to prevent the radioactive seeds from dislodging or falling out prior to insertion into the body.

Prior to insertion, a solid wire stylet is coaxially introduced into the proximal end of the cannula to rest upon the stack of seeds and spacers at the delivery tip of the needle. The physician then inserts the needles one-by-one into the patient, and once inserted into the body to the proper position, the stylet is held firm and the cannula of the needle is moved towards the proximal end of the stylet. This motion deposits the radioactive seeds, spacers, and the bone wax needle plug into the body in a track or line as the cannula is pulled back, leaving the seeds to permanently reside in the body as the radioactive dose decays over the treatment time.

1. Potential Risks of Commercializing the Use of Bone Wax or Reformulated "Faux Bone Wax" in Soft Tissue

Although physicians have used bone wax "off-label" in brachytherapy procedures, it is doubtful that reliable conclusions regarding safety could be extrapolated from associated data in that field (to the extent that it exists) because the migration of radioactive seeds and/or bone wax plugs is not routinely checked beyond the initial "same day" chest x-ray and a subsequent 30 day follow-

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[9] *See* Subir Nag, M.D., *et al.*, *Pulmonary Embolization of Permanently Implanted Radioactive Palladium-103 Seeds for Carcinoma in the Prostate*, 39 Int. Journal of Radiation Oncology Biol. Phys. 667 (1997) (Att. 7).

up x-ray of the patient's lungs. However, published studies[10] show that seed migration can occur anywhere from 1 to 127 days after the brachytherapy procedure (a full 3 months beyond the standard 30 day follow-up). Notably, we did not identify any studies, to date, that have focused on bone wax migration and the mid- to long-term effects of bone wax residing in soft tissues after the initial brachytherapy procedure.

Due to this lack of data on potential migration beyond the typical brachytherapy follow-up period, and associated complications, we have grave concerns about the safety of commercial brachytherapy kits that use non-absorbable bone wax or reformulated "faux bone wax" off-label as needle plugs.

Disturbingly, there is substantial scientific literature on the negative effects of the use of bone wax and its ensuing complications in other fields of medical practice (cited and discussed in detail in Section C(1)(b)), indicating that bone wax does migrate to soft tissues throughout the body and can cause chronic inflammation (granulomatis infection), marked foreign body reaction, sarcomas (*e.g.*, angiosarcomas), epistaxis, allergic reactions, sigmoid sinus thrombosis, foreign body venous embolization, and pulmonary complications. Moreover, it is believed that bone wax left in the body has even contributed to quadriplegia.[11]

Further, multiple brachytherapy oncology articles have reported that seed migration from the prostate gland to the lungs is common, and some experts estimate that it occurs in 18-36% of all implant procedures.[12] Given this high incidence, and the fact that the bone wax or reformulated "faux bone wax" plug necessarily resides in front of the line of seeds within each needle, it is reasonable to conclude that the bone wax plug may also commonly migrate to the lungs.

Given the history of bone wax complications arising from its inadvertent displacement into soft tissue, it is even more disconcerting that certain manufacturers have introduced to the market commercial brachytherapy kits that use plugs formed from what is, to the best of our knowledge, an untested reformulation of bone wax. We can only opine that the manufacturers of kits with bone wax plugs made the switch to these reformulated "faux bone wax" plugs because the bone wax plugs previously used proved to be temperature unstable during shipping. It is our understanding that these manufacturers developed the reformulated "faux bone wax" by reformulating the compounds in traditional bone wax and adding fibrous substances to raise the

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[10] See, e.g, Subir Nag, M.D., *et al.*, *Pulmonary Embolization of Permanently Implanted Radioactive Palladium-103 Seeds for Carcinoma in the Prostate*, 39 Int. Journal of Radiation Oncology Biol. Phys. 667 (1997) (Att. 7).

[11] *See infra*, discussion at Section C(1)(b).

[12] *See infra*, discussion at Section C(1)(b).

product's melting point and to make the product less sticky and more solid at higher temperatures.

Reformulated "faux bone wax," at minimum, poses the same safety hazards as bone wax because, like bone wax, it is non-absorbable. Therefore, like bone wax, it may migrate to undesirable locations in the body, where it can lodge permanently and cause adverse events. Moreover, we understand that reformulated "faux bone wax" is specifically formulated to maintain its form at higher temperatures, and thus, it is likely to maintain its form at body temperatures. Because it is more solid and less sticky than traditional bone wax at body temperatures, reformulated "faux bone wax" should be even more likely than bone wax to migrate independently from the seeds. Reformulated "faux bone wax" also could pose additional safety hazards because, to our knowledge, its new chemical formula(s) has not been clinically tested, and it does not have a history of any type of use in the body.[13]

2. Requested Actions by the FDA

Accordingly, we believe commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs present an "unreasonable and substantial risk of illness or injury," such that FDA should take immediate action to ban the devices under Section 516(a)(1) of the FFDCA.[14] Patients would continue to have access to commercial brachytherapy kits that do not use plugs at all, or use synthetic bioabsorbable plugs.[15] Importantly, the material used in synthetic bioabsorbable plugs, unlike bone wax or reformulated "faux bone wax," is well-established as safe for use in soft tissue,[16] and therefore, does not pose the same risks as bone wax or reformulated "faux bone wax."

At minimum, FDA should require manufacturers of commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" plugs to obtain PMA approval prior to commercial distribution. Such kits are new devices that raise completely different issues from other legally marketed devices. Thus, we believe such kits should be regulated as class III devices, and should require PMA approval.[17]

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[13] *See infra*, discussion at Section C(1)(b).

[14] 21 U.S.C. § 360f(a)(1) (Supp. 2004).

[15] For example, Imagyn (succeeded by Bard), Implant Sciences, IsoAid, Oncura, North American Scientific, and Theragenics, among others, all sell brachytherapy kits that do not use bone wax or reformulated "faux bone wax" needle plugs. *See* Literature for Brachytherapy Kits Without Bone Wax or "Faux Bone Wax" Plugs (Att. 8).

[16] *See infra*, at Section C(2)(b).

[17] *See* 21 U.S.C. § 360e (Supp. 2004).

Indeed, we do not believe such devices are eligible for 510(k) clearance at all. The overwhelming scientific data indicating that the use of bone wax or reformulated "faux bone wax" needle plugs in commercial brachytherapy kits is dangerous, in and of itself, is evidence that manufacturers cannot show that such kits are "substantially equivalent" to predicate devices, as required under the 510(k) process.[18] If manufacturers were required to file PMAs, then they would have to prove that the device in its entirety - including all of the components, such as needle plugs - presents a "reasonable assurance of safety,"[19] as the FFDCA requires.[20]

In addition, regardless of which approach FDA decides to take, it should also rescind any current "substantial equivalence" orders (*i.e.*, 510(k) clearances) for such brachytherapy kits - and remove from the market any brachytherapy kits currently marketed in the absence of 510(k) clearance or PMA approval.

B. Actions Requested

1. FDA should immediately take action to ban the sale of commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs; or

   FDA should immediately require manufacturers of commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs to obtain PMA approval for their kits, rather than 510(k) clearance, prior to commercial distribution; and

2. Regardless of whether FDA decides to ban commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" plugs, or require PMAs, FDA should also rescind any current "substantial equivalence" orders (*i.e.*, 510(k) clearances) for brachytherapy kits that use bone wax or reformulated "faux bone wax" – and remove from the market any brachytherapy kits currently marketed in the absence of 510(k) clearance or PMA approval.

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[18] *See* 21 U.S.C. §§ 360(k), 360c(f), (i) (Supp. 2004); 21 C.F.R. § 807.100(b) (2004); Premarket Notification 510(k): Regulatory Requirements for Medical Devices, HHS Publication FDA, 95-4158 (Aug. 1995).

[19] Section 515(d) of the FFDCA requires FDA to determine whether a device has a "reasonable assurance of safety," in deciding whether to grant or deny a PMA. *See* 21 U.S.C. § 360e(d) (Supp. 2004).

[20] In keeping with FDA's biocompatibility guidance document, for a PMA, manufacturers of brachytherapy kits with bone wax or reformulated "faux bone wax" plugs also would have to demonstrate that the bone wax would not cause adverse effects. *See* Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices (May 1, 1995), http://www.fda.gov/cdrh/g87-1.html.

C. Statement of Grounds

1. Commercial Brachytherapy Kits with Bone Wax or Reformulated "Faux Bone Wax" Needle Plugs Present an Unreasonable and Substantial Risk of Injury, and Should Be Banned

a. Legal Standard to Ban Medical Devices

Section 516(a)(1) of the FFDCA provides that FDA may initiate proceedings to promulgate a regulation to ban a device if the device "presents substantial deception or an unreasonable and substantial risk of illness or injury" that cannot be corrected by a labeling change.[21] The regulations implementing that section state that, in determining whether a device poses a substantial risk, the FDA must consider whether the risk is "important, material or significant" in relation to the benefit from the device to the public health.[22]

The manner in which FDA has interpreted Section 516(a)(1) of the FFDCA in the past is instructive. In 1983, FDA banned prosthetic hair fibers, after determining based on scientific literature and reports of adverse events, among other things, that there were no conditions under which the devices could be safely marketed.[23] According to FDA, prosthetic hair fibers met the standard in Section 516(a)(1) of the FFDCA because there could be:

> no benefit to the public health from continued marketing of prosthetic hair fibers, and the . . . risk posed by their continued marketing is important, material, and significant, considering the severity of the infections, illnesses, or injuries caused by their implantation.[24]

The injuries caused by the prosthetic hair fibers were largely due to foreign body reactions, and they included breakage of the fibers at the scalp line, permanent additional loss of natural hair, itchiness, facial swelling, severe pain, infections, severe and punctate scarring, and even long-term risk of developing cancer. Some of these injuries even required corrective medical or surgical treatment.

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[21] *See* 21 U.S.C. § 360f(a)(1) (Supp. 2004).

[22] *See* 21 C.F.R. § 895.21(a)(1) (2004). FDA specifically declined an opportunity to define "unreasonable" as it is used in Section 516(a)(1) of the FFDCA, stating that the legislative history only defined the term "substantial." *See* 44 Fed. Reg. 29214, 29215 (May 18, 1979).

[23] *See* 48 Fed. Reg. 25126, 25127-28 (June 3, 1983).

[24] *Id.*

Notably, in that case, FDA specifically stated that it did not have or need any information regarding the incidence of the adverse events because the risk of infection with prosthetic hair fibers was inherent and the adverse events were severe.[25] The fact that it did not need any information regarding incidence is particularly instructive, given that FDA was justifying a "ban" with a "special effective date" and therefore had to meet a higher legal standard, showing that the risk posed by the devices presented an "unreasonable, direct, and substantial danger to the health of individuals."[26]

b. Commercial Brachytherapy Kits with Bone Wax or Reformulated "Faux Bone Wax" Needle Plugs Meet the Legal Standard for a Ban

In this case, as with the prosthetic hair fibers, overwhelming scientific data indicates that commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" as needle plugs present an "unreasonable and substantial risk of illness or injury."[27] As detailed below, as with prosthetic hair fibers, the risk presented is important, material, and significant, given the severity of the illnesses and injuries that the devices can cause. Moreover, as with prosthetic hair fibers, this risk cannot be avoided through labeling because the risk is inherent when bone wax or reformulated "faux bone wax" are used off-label as needle plugs in commercial brachytherapy kits.

Bone wax does not absorb into the body.[28] As a result, bone wax used during medical procedures has caused chronic inflammation (granulomatis infection), marked foreign body reaction, sarcomas/angiosarcomas (*i.e.*, blood vessel cancer), epistaxis, allergic reactions, sigmoid sinus thrombosis, and pulmonary complications, and it has even contributed to paraplegia and quadriplegia.[29] Bone wax, like the prosthetic hair fibers, is a foreign object in the body, and as

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[25] *See id.*

[26] *See id. See also* 21 C.F.R. § 895.30 (2004) (regarding special effective dates).

[27] 21 U.S.C. § 360f(a)(1) (Supp. 2004).

[28] Ole-Gunnar, M.D. *et al.*, *Complications Secondary to the Use of Standard Bone Wax in Seven Patients*, 32 The Journal of Ankle and Foot Surgery 505 (1993) (acknowledging that bone wax is not absorbed) (Att. 9).

[29] Ole-Gunnar, M.D. *et al.*, *Complications Secondary to the Use of Standard Bone Wax in Seven Patients*, 32 The Journal of Ankle and Foot Surgery 505 (1993) (concluding, based on seven cases involving foot and shoulder surgery, that bone wax can cause chronic inflammation and foreign body reaction) (Att. 9); James Aurelio, D.D.S., *et al.*, *Foreign-body reaction to bone wax*, 58(1) Oral surgery, Oral Medicine, Oral Pathology 98 (1984) (concluding, based on a case study where bone wax used during mouth surgery caused chronic inflammation, that "[w]hen bone wax is left in tissue, it stimulates or elicits an inflammatory response and a foreign-body reaction") (Att. 10); Blake A. Morrison, M.D., *Soft tissue sarcomas of the extremities*, 16 BUMC Proceedings 285 (2003) ("The link between foreign bodies and sarcoma has

such triggers the body's defense system, acting as a catalyst for many of these complications, such as granulomatous infections, epistaxis, and allergic reactions, as well as sarcomas.[30] Importantly, these significant adverse events are documented not only by the literature, but also by FDA's medical device reporting ("MDR") database, which contains a number of reports from manufacturers, importers, and user facilities.[31]

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been described since the 1880s and has been well-studied in rats. Rare human cases have also been described, involving [among other things] . . . bone wax . . . .") (Att. 11); Bayram Cirak, M.D. and Oscan Ulna, M.D., *Estrogenic quadriplegia and bone wax*, 92 J. Neurosurgery: Spine 248 (April 2000) (reporting a case where the physicians believed that the use of bone wax to stop bleeding during an operation for an acoustic neuronal, combined with a cervical spine epidural hecatomb caused quadriplegia, and acknowledging that bone wax has been reported to cause "granulomatous infection, epistaxis, allergic reaction, and intracranial granuloma") (Att. 12); W.K. Low and C.S. Sim, *Bone Wax Foreign Body Granuloma in the Mastoid*, 64 ORL 38 (2002) (reporting a case of bone wax granuloma in the mastoid, and noting that using bone wax in surgery in and around the mastoid can cause complications, such as "granulomatous foreign body reaction, sigmoid sinus thrombosis, wound infection, and even foreign body venous embolization") (Att. 13); Farah Bhatti, BestBets: Best Evidence Topics, Literature Review: Does Liberal Use of Bone Wax Increase the Risk of Mediastinitis, http://www/ bestbets.org/cgi-bin/bets.pl?record=00604 ("[A]nimal studies have shown that Bone wax can embolize to the lungs, that Bone wax markedly reduces the inoculum of Staphlococcus Aureus required to cause osteomylitis, and that Bone wax is still present in large quantities 4 weeks post-operatively") (Att. 14); Rakesh B. Patel, M.D., *et al.*, *Bone wax as a cause of foreign body granuloma in the berebellopontine angle*, 92 J. Neurosurg 362 (2000) (reporting a case of intracranial foreign body granuloma related to the use of bone wax) (Att. 15); Francis Robicsek, M.D., *The Embolization of Bone Wax from Sternotomy Incisions*, 31 Annals of Thoracic Surgery 357 (1980) (concluding based on clinical observations and animal studies that it is probable that bone wax embolization to the lung that occurs in animals also occurs in clinical settings) (Att. 16); Belen Carsi, M.D., Ph.D., *Angiosarcoma*, 2 eMedicine Journal (Dec. 2001) ("Some angiosarcomas are associated with foreign material introduced to the body . . . [such as] Dacron, shrapnel, steel, plastic graft material, surgical sponges, and bone wax") (Att. 17).

[30] *See, e.g.*, Ole-Gunnar, M.D. *et al.*, *Complications Secondary to the Use of Standard Bone Wax in Seven Patients*, 32 The Journal of Ankle and Foot Surgery 505 (1993) (Att. 9); James Aurelio, D.D.S., *et al.*, *Foreign-body reaction to bone wax*, 58(1) Oral Surgery, Oral Medicine, Oral Pathology 98 (1984) (Att. 10); Blake A. Morrison, M.D., *Soft tissue sarcomas of the extremities*, 16 BUMC Proceedings 285 (2003) (Att. 11); Bayram Cirak, M.D. and Ozkan Unal, M.D., *Iatrogenic quadriplegia and bone wax*, 92 J. Neurosurg: Spine 248 (April 2000) (Att. 12); W.K. Low and C.S. Sim, *Bone Wax Foreign Body Granuloma in the Mastoid*, 64 ORL 38 (2002) (Att. 13); Rakesh B. Patel, M.D., *et al.*, *Bone wax as a cause of foreign body granuloma in the berebellopontine angle*, 92 J. Neurosurg 362 (2000) (Att. 15); Belen Carsi, M.D., Ph.D., *Angiosarcoma*, 2 eMedicine Journal (Dec. 2001) (Att. 17).

[31] *See, e.g.*, MDR Database, No. M751327, dated April 4, 1996 (granuloma) (Att. 18); MDR Database, No. M476758, dated Feb. 7, 1994 (paraplegia) (Att. 19); MDR Database, No. M213158 ("series of subcutaneous infections involving sternal and leg wounds") (Att. 20); MDR Database, No. M178314, dated Dec. 1, 1989 (infection) (Att. 21); MDR Database, No. M178143, dated Nov. 29, 1989 (infection) (Att. 22); MDR Database, No. M154511, dated May 20, 1988 (reoperation due to post-operative drainage) (Att. 23); MDR Database, No. M125866, dated July 15, 1986 (sternum infection) (Att. 24); MDR Database, No. M117354, dated Jan. 13, 1986 (post-operative infection in three patients) (Att. 25); MDR Database, No. M101751, dated Feb. 15, 1985 (dental staphylococcus infection) (Att. 26).

Notably, the reports in the MDR database are only representative of the extent of the problem. FDA itself concedes that the MDR database has "serious shortcomings." Medical Device Reporting ("MDR") General Information,

In addition, studies such as Robicsek *et al.* (1980) and W.K. Low and C.S. Sim (2002), indicate that bone wax can embolize to soft tissue and the venous system, causing additional complications.[32] In Robicsek *et al.* (1980), for example, the researchers demonstrated that bone wax migrates into soft tissues of the lung from remote surgical sites, by tagging bone wax used in animal procedures. That study confirmed the research team's clinical observation that abandoning the use of bone wax as a hemostatic agent in sternotomy incisions led to a drop in pulmonary complications.[33] Indeed, Dr. Robicsek later stated:

> [W]e found not only that the bone wax has a potential of embolizing into the lungs but also that it did not decrease blood loss in patient cohorts where bone wax was not used. Adding to this the potential of increase in infections, one may ask the question why should anybody use bone wax at all?[34]

Dr. Robicsek also added:

> [I]f anybody ever looked at surgical "bone wax" under a microscope and could see all the insect ova, legs and fragments of wings, - he would think it over twice before using bone wax again![35]

Notably, the adverse reactions enumerated above are similar in severity to those caused by prosthetic hair fibers, and some of the reactions, like those caused by prosthetic hair fibers, even required additional corrective operations or procedures.[36]

FDA Website, http://www.fda.gov/cdrh/mdr/mdr-general.html. Notably, the MDR database does not include complaints from physicians and consumers. According to FDA, research has shown that "less than one percent of device problems occurring in hospitals are reported to FDA, and the more serious the problem with a device, the less likely it was to be reported." *Id.*

[32] Francis Robicsek, M.D., *The Embolization of Bone Wax from Sternotomy Incisions*, 31 Annals of Thoracic Surgery 357 (1980) (Att. 16); W.K. Low and C.S. Sim, *Bone Wax: Foreign Body Granuloma in the Mastoid*, 64 ORL 38 (2002) (Att. 13).

[33] Francis Robicsek, M.D., *The Embolization of Bone Wax from Sternotomy Incisions*, 31 Annals of Thoracic Surgery 357 (1980) (Att. 16); *see also* Farah Bhatti, BestBets: Best Evidence Topics, Literature Review: Does Liberal Use of Bone Wax Increase the Risk of Mediastinitis, http://www/ bestbets.org/cgi-bin/bets.pl?record=00604 (concluding based on a literature review that bone wax can embolize to the lungs and that animal studies indicate strong reasons for concern over the liberal use of bone wax) (Att. 14).

[34] Farah Bhatti, BestBets: Best Evidence Topics, Literature Review: Does Liberal Use of Bone Wax Increase the Risk of Mediastinitis, http://www/ bestbets.org/cgi-bin/bets.pl?record=00604 (with a statement from Dr. Robicsek in Appendix A) (Att. 14).

[35] *Id.*

The bone wax used in prostate brachytherapy procedures is likely to have the same adverse effects observed in the other medical procedures, or worse. Multiple brachytherapy oncology articles have reported that seed migration to the lungs is common, and some experts have estimated that seed migration occurs in 18-36% of all implant procedures.[37] Given this high incidence, and the fact that the bone wax or reformulated "faux bone wax" plug necessarily resides in front of the line of seeds within each needle, it is reasonable to conclude that the bone wax plug also commonly migrates to the lungs.

The amount of bone wax left inside a patient during a brachytherapy procedure is substantial. As mentioned, during the typical prostate implant procedure, 15 to 60 brachytherapy needles are inserted into the prostate gland, and therefore, 15 to 60 bone wax pellets are left inside the gland and in the surrounding area. Each bone wax plug in a commercially prepared kit is typically 4 to 5 mm long and approximately 1.2 mm in diameter, and each has the individual potential to migrate to the lungs.

Importantly, the package insert for Ethicon bone wax, a standard in the bone wax industry, specifically cautions that "excess Bone Wax should be removed from an operative site."[38] Obviously, that does not happen when bone wax is used in brachytherapy procedures. Moreover, the package insert specifically warns against resterilizing the product, which generally happens when bone wax is used in commercial brachytherapy kits.[39]

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[36] *See, e.g.*, MDR Database, No. M125866, dated July 15, 1986 (sternum infection) (Att. 24); MDR Database, No. M751327, dated Apr. 4, 1996) (Att. 18); MDR Database, No. M178314, dated Dec. 1, 1989 (infection) (Att. 21).

[37] Robert A. Older, *et al.*, *Radioactive Implant Migration In Patients Treated for Localized Prostate Cancer with Interstitial Brachytherapy*, 165 The Journal of Urology 1590 (2001) (concluding that the incidence of pulmonary embolization of radioactive seeds after prostate brachytherapy is 29%) (Att. 27); Murali K. Ankem, *Implications of Radioactive Seed Migration to the Lungs After Prostate Brachytherapy*, 59(4) Urology 555 (2002) (finding that radioactive seed migration to the lungs occurred in 36.2% of brachytherapy patients who had chest radiographs) (Att. 28); Brian J. Davis, *Prostate Brachytherapy Seed Migration to the Right Ventricle Found at Autopsy Following Acute Cardiac Dysrhythmia*, 164 The Journal of Urology 1661 (2000) ("vascular migration of radioactive seeds to the lungs following permanent prostate brachytherapy is a recognized phenomenon. We report a case in which seeds became lodged in the right ventricle") (Att. 29); Subir Nag, M.D., *et al.*, *Pulmonary Embolization of Permanently Implanted Radioactive Palladium 103 Seeds for Carcinoma in the Prostate*, 39 Int. Journal of Radiation Oncology Biol. Phys. 667 (1997) (reporting that seeds migrated to the lungs in 18% of the patients who had prostate brachytherapy) (Att.7); Brian J. Davis, *et al.*, *Prostate Brachytherapy Seed Migration to a Coronary Artery Found During Angiography*, 168 The Journal of Urology 1103 (2002) (involving a single case report) (Att. 30).

[38] *See, e.g.*, Ethicon Bone Wax Package Insert (Att. 31).

[39] *See id.*

Given that approximately 232,090 American men are expected to be diagnosed with prostate cancer in 2005 alone,[40] and that approximately 40,000 of those men will choose to undergo brachytherapy treatment,[41] the off-label use of bone wax or reformulated "faux bone wax" in commercial brachytherapy kits potentially poses a massive public health threat. The extent of this threat, however, cannot yet be known. To our knowledge, there have been no clinical trials testing the safety of such commercial kits, many (if not all) of which have been marketed without PMAs or 510(k) clearances. Moreover, although some physicians have used bone wax plugs "off-label," any associated data (to the extent that it exists) would likely be anecdotal. Further, prostate brachytherapy procedures have only been performed regularly for the last 9 to 10 years, and it can take years for complications to manifest.

The use of reformulated "faux bone wax" is even more alarming because in addition to being non-absorbable, it is a completely new product on the market. As mentioned, it has come to our attention that certain manufacturers may have introduced to the market commercial brachytherapy kits that use reformulated "faux bone wax" plugs. We are of the opinion that manufacturers of kits with bone wax plugs made the switch because the bone wax plugs proved to be unstable during shipping. Therefore, we believe they developed reformulated "faux bone wax" by reformulating the compounds and adding fibrous substances, to raise the product's melting point and to make the product less sticky and more solid at higher temperatures. Because it is more solid and less sticky than traditional bone wax at high temperatures, such as body temperatures, reformulated "faux bone wax" should be even more likely than bone wax to migrate independently from the seeds. Further, to our knowledge, reformulated "faux bone wax" has been used only in recently distributed commercial brachytherapy kits, and has impacted only approximately a few thousand patients at this point. Therefore, we believe it does not have a history of use in the human body.

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[40] *See, e.g.*, American Cancer Society Website (estimating that 232,090 American men will be diagnosed with prostate cancer in 2005), http://www.cancer.org/docroot/CRI/content/CRI_2_2_1X_How_many_men_get_prostate_cancer_36.asp?sitearea= (Att. 5).

[41] Louis Potters, M.D., *Permanent Prostate Brachytherapy in Patients with Clinically Localized Prostate Cancer*, Men's Health and Cancer, malecare, http://www.malecare.org/new_page_93.htm (the 40,000 figure is based on a 2001 estimate) (Att. 6).

2. FDA Should Require Manufacturers of Commercial Brachytherapy Kits that Use Bone Wax or Reformulated "Faux Bone Wax" Needle Plugs to Obtain PMA Approval Prior to Commercial Distribution

a. Overview

At minimum, given the new safety issues raised, FDA should require manufacturers of commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs to obtain PMA approval prior to commercial distribution. Such kits are new devices that raise completely different issues from other legally marketed devices. Thus, we believe such kits should be regulated as class III devices, and should require PMA approval.[42]

Indeed, we believe that commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs are not eligible for 510(k) clearance at all. The overwhelming scientific data indicating that commercial brachytherapy kits using bone wax and reformulated "faux bone wax" needle plugs are dangerous, in and of itself, is evidence that manufacturers cannot show that that such kits are "substantially equivalent" to any predicate device,[43] as required under the 510(k) process.[44]

If manufacturers were required to file PMAs, then they would have to prove that the device in its entirety – including all of the components, such as needle plugs - present a "reasonable assurance of safety."[45]

b. Commercial Brachytherapy Kits with Bone Wax or Reformulated "Faux Bone Wax" Needle Plugs Are Not "Substantially Equivalent" to Any Lawfully Marketed Device Prior to April 2004

To meet the "substantial equivalence" standard, a new device with different technological characteristics from a predicate device must: (1) not raise new questions of safety and

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[42] *See* 21 U.S.C. § 360e (Supp. 2004).

[43] *See id.* §§ 360e(a), 360c(f); Premarket Notification 510(k): Regulatory Requirements for Medical Devices, HHS Publication FDA, 95-4158 (Aug. 1995).

[44] *See* 21 U.S.C. §§ 360(k), 360c(f), (i) (Supp. 2004); 21 C.F.R. § 807.100(b) (2004); Premarket Notification 510(k): Regulatory Requirements for Medical Devices, HHS Publication FDA, 95-4158 (Aug. 1995).

[45] Section 515(d) of the FFDCA requires FDA to determine whether a device has a "reasonable assurance of safety," in deciding whether to grant or deny a PMA. *See* 21 U.S.C. § 360e(d) (Supp. 2004).

effectiveness, and (2) be as safe and as effective as the legally marketed device.[46] As such, FDA simply cannot make a legitimate finding that commercial brachytherapy kits using bone wax or reformulated "faux bone wax" needle plugs are "substantially equivalent" to any lawfully marketed predicate device.

As an initial matter, commercial brachytherapy kits using bone wax or reformulated "faux bone wax" needle plugs have "different technological characteristics" from any predicate device. No legally marketed commercial brachytherapy kits using bone wax or reformulated "faux bone wax" needle plugs were cleared by the FDA prior to April 2004. The only commercial brachytherapy kits that were cleared through the 510(k) process before April 2004, were: (1) a brachytherapy kit using a needle plug made of bioabsorbable synthetic suture material (which has been implanted in the prostate for many years in the form of "seed spacers"),[47] and (2) a brachytherapy kit that obviates the need for plugs altogether with a sophisticated needle design.[48] Further, brachytherapy kits with bone wax or reformulated "faux bone wax" plugs, by definition have at least three components – brachytherapy needles, seeds, and plugs – and therefore, they are technologically different from any device that contains only a subset of those components.[49]

Accordingly, to show "substantial equivalence," manufacturers would have to demonstrate that the kits: (1) do not raise any new questions of safety and effectiveness, and (2) are as safe and effective as a predicate device. We believe manufacturers cannot do so because bone wax and reformulated "faux bone wax" plugs raise questions of safety and efficacy that are exceedingly

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[46] *See id.* § 360c(i); 21 C.F.R. § 807.100(b) (2004); Premarket Notification 510(k): Regulatory Requirements for Medical Devices, HHS Publication FDA, 95-4158 (Aug. 1995) (emphasis added).

[47] *See, e.g.*, World Wide Medical Technologies, 510(k) No. K022389, May 6, 2003 (Att. 32).

[48] *See, e.g.*, Imagyn Medical Technologies, 510(k) No. K010166, Dec. 3, 2001 (Att. 33).

[49] To the extent that there are commercial brachytherapy needles plugged with bone wax or reformulated "faux bone wax" on the market, they should be regulated as class III devices. They should not be governed by 21 C.F.R. § 892.5650, which regulates "manual radionuclide applicator systems" (*e.g.*, unplugged brachytherapy needles and their component parts and accessories) as Class I, 510(k) exempt devices. In 1982, FDA classified manual radionuclide applicators (including the generic device with components and accessories), under 21 C.F.R. § 892.5650, as class I devices because it could not identify any risks to health. *See* 47 Fed. Reg. 4406, 4438 (Jan. 29, 1982). However, at that time brachytherapy had not yet been performed. Indeed, the first brachytherapy procedures were performed in 1985. *See* John E. Sylvester, M.D., *Modern Brachytherapy*, Oncology Issues (May/June 2002) (Att. 34). Thus, we do not believe FDA could have contemplated that brachytherapy needles plugged with bone wax could ever fall under that section. Moreover, brachytherapy needles plugged with bone wax or reformulated "faux bone wax" raise the same safety issues as brachytherapy kits because they inject non-absorbable plugs into the body.

different from those raised by the predicate brachytherapy kits, which either do not use plugs at all or use plugs made of bioabsorbable synthetic suture material.

As summarized above, overwhelming scientific data indicates that "bone wax" plugs present significant safety risks because they do not absorb into the body. As such, they could trigger the body's defense system, acting as a catalyst for many complications, including chronic inflammation (granulomatis infection), marked foreign body reaction, sarcomas/angiosarcomas (*i.e.*, blood vessel cancer), epistaxis, allergic reactions, sigmoid sinus thrombosis, foreign body venous embolization, and it could even contribute to quadriplegia, among other things.[50] In addition, the plugs of bone wax could migrate to the lungs where they could cause further complications.[51] Reformulated "faux bone wax" may be even worse. We believe reformulated "faux bone wax" poses the same safety risks as bone wax because it cannot absorb into the body, and it may pose unknown additional risks, given that it does not have a well-established history of use in the body for any purpose (if any history at all).[52]

The brachytherapy kits on the market that do not use bone wax or reformulated "faux bone wax" do not raise these safety issues because they either do not use plugs at all or the plugs are made of synthetic suture material that absorbs into the body.[53] Notably, bioabsorbable synthetic suture material, unlike bone wax or reformulated "faux bone wax," is well-established as safe for use in soft tissue.

For example, the FDA cleared synthetic bioabsorbable sutures, for use in soft tissue at least eight years ago.[54] In addition, FDA specifically cleared the use of synthetic suture for use as seeding spacer material in brachytherapy kits over five years ago,[55] and has since cleared a brachytherapy

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[50] *See supra*, discussion at Section C(1)(b) herein.

[51] *See supra*, discussion at Section C(1)(b) herein.

[52] *See supra*, discussion at Section C(1)(b) herein.

[53] *See* Labeling Information for Monocryl (indicating that bioabsorbable synthetic suture, when used as a traditional suture, could lead to significantly less severe adverse reactions, such as "infection" and "minimal acute inflammatory tissue reaction") (Att. 35).

[54] *See, e.g.*, Ethicon, Inc., 510(k) No. K964072, Dec. 18, 1996 (Att. 36); *see also* Monocryl (Poliglecaprone 25) Information Sheet (Att. 37).

[55] *See* Indigo Medical Co., 510(k) No. K992262, Oct. 4, 1999 (Att. 38); *see also* World Wide Medical Technologies, 510(k) No. K991344, Nov. 5, 1999 (Att. 39).

kit that uses synthetic suture to plug the brachytherapy needles.[56] In stark contrast, to the best of our knowledge, bone wax and reformulated "faux bone wax," as stand-alone products, have been cleared only to stop bone bleeding locally[57] - they have never been cleared for use in soft tissue.

There are a number of companies advertising commercial brachytherapy kits that promote the use of bone wax or reformulated "faux bone wax" plugs.[58] Commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs overtly raise questions of safety that are new and different from those raised by the brachytherapy kits that were on the market prior to April 2004, and pose a potential public health threat. Accordingly, any such brachytherapy kit should require PMA approval, rather than a 510(k) clearance, prior to commercial distribution.

c. **FDA May Have Cleared Two New Brachytherapy Kits Via the 510(k) Process in April and July 2004, that May Potentially Use Bone Wax or Reformulated "Faux Bone Wax" Needle Plugs**

Publicly available information suggests that two recently cleared brachytherapy kits may potentially use bone wax or reformulated "faux bone wax" needle plugs. As shown above, we believe such kits would require a PMA, rather than a 510(k), because they raise questions of safety that are different from those raised by brachytherapy kits with 510(k) clearance prior to April 2004. Accordingly, to the extent that the two kits contain bone wax or reformulated "faux bone wax" needle plugs, we believe that they were likely cleared in error.

Based on the information available, FDA may have overlooked the fact that these kits potentially use bone wax or reformulated "faux bone wax" plugs and/or was unaware of the safety implications. Indeed, the information provided in the 510(k) summaries for the devices suggest that needle plugs are needed for the kits, but fail to mention the type of needle plugs used and fail to cite predicate devices that use bone wax or reformulated "faux bone wax" needle plugs.

On July 16, 2004, FDA cleared a brachytherapy kit submitted by International Brachytherapy, S.A. ("IBt"), 510(k) No. K041702. The only publicly available information about the IBt kit is the 510(k) summary, which makes no mention of the type of plug used with the brachytherapy needles. The 510(k) summary merely styles the new device, EZ-Pak™ , as "a packaging change"

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[56] *See* World Wide Medical Technologies, 510(k) No. 022389, May 6, 2003 (Att. 32).

[57] *See, e.g.*, United States Surgical Corporation, 510(k) No. K971680, Oct. 24, 1997 (claiming "substantial equivalence" with Johnson & Johnson's Ethicon™ (preamendment) and Lukens™ Bone Wax (K791405)) (Att. 1); CP Medical, Inc., 510(k) No. K024372, June 19, 2003 (Att. 2).

[58] *See, e.g.*, Miscellaneous Promotional Material for Kits Using Bone Wax or "Faux Bone Wax" Plugs (Att. 4).

to previous products marketed by that company – *i.e.*, Intersource-103, Intersource-125, and Interstrand® . Indeed, a reading of the 510(k) summary for EZ-Pak™ and the 510(k) summary for Interstrand® suggests that EZ-Pak™ is Interstrand® (*i.e.*, a strand containing radioactive seeds (Intersource®) and spacers) "repackaged" into brachytherapy needles.

However, this "repackaging" is not as incidental as the 510(k) summary for EZ-Pak™ suggests. It is extraordinarily material because the "repackaging" necessitates the use of a plug to secure the contents of the needle during shipping and subsequent handling by the surgical team members, as well as additional sterilization procedures – both of which potentially have attendant safety risks, particularly if the plug used is made of bone wax or reformulated "faux bone wax." (As mentioned, the package insert for Ethicon bone wax specifically cautions against resterilizing the product).[59]

Yet, the 510(k) summary fails to reference any predicate devices[60] other than Intersource-103, Intersource-125, and Interstrand® , none of which utilizes bone wax or reformulated "faux bone wax" plugs.[61] In fact, the 510(k)s for those devices specifically state that the only materials that come into contact with the body are titanium and, in the case of Interstrand® , suture material.[62] There is no mention of bone wax.

In this instance, we believe that the IBt brachytherapy kit, EZ-Pak™ , does use bone wax or reformulated "faux bone wax" needle plugs – despite the omission in the 510(k) summary – because the description of Interstrand® in IBt's own advertising material contemplates the use of the strand with a bone wax plug as follows:

> "Interstrand® consists of 10 Intersource® seeds threaded into a monofilament absorbable suture. The seeds are spaced 1 cm apart measured center to center. Interstrand® easily penetrates the standard bone wax plug,

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[59] *See* Ethicon Bone Wax Package Insert (Att. 31).

[60] *See* IBt EZ-Pak Brachytherapy Kit, 510(k) No. K041702, July 16, 2004 (Att. 40).

[61] *See* IBt Interstrand, 510(k) No. K011155, July 12, 2001 (specifically stating that the only materials contacting the body are titanium and suture material) (Att. 41); IBt Intersource-125, 510(k) No. K984235, June 9, 1999 (specifically stating that the only material contacting the body is titanium) (Att. 42); IBt Intersource-103 (Interseed), 510(k) No. K973328, Dec. 10, 1998 (same) (Att. 43).

[62] *See* IBt Interstrand, 510(k) No. K011155, July 12, 2001 (specifically stating that the only materials contacting the body are titanium and suture material) (Att. 41); IBt Intersource-125, 510(k) No. K984235, June 9, 1999 (specifically stating that the only material contacting the body is titanium) (Att. 42); IBt Intersource-103 (Interseed), 510(k) No. K973328, Dec. 10, 1998 (same) (Att. 43).

> minimizes seed migration, and reduces prep time .... Benefits ... Easily Penetrates Bone Wax."[63]

The 510(k) for the brachytherapy kit submitted by BEBIG Isotopen-und Medizintechnik GmbH ("BEBIG"), which was cleared by FDA on April 8, 2004, is silent with regard to whether the kit uses needle plugs and with regard to the type of needle plug used[64] – despite the fact that a needle plug would likely be necessary to secure the contents of the needle during shipping and subsequent handling by the surgical team members. Indeed, the 510(k) summary specifically compares the "packaging" of the BEBIG brachytherapy kit to the strand that is cited as the predicate device, but it only mentions the "implantation needle," not the needle plug. Moreover, none of the predicate devices cited use bone wax or reformulated "faux bone" wax needle plugs.

3. FDA Should Rescind Any Current "Substantial Equivalence" Order for Brachytherapy Kits that Use Bone Wax or Reformulated "Faux Bone Wax" – And Remove from the Market Any Brachytherapy Kits Currently Marketed in the Absence of 510(k) Clearance or PMA Approval

Regardless of whether FDA decides to ban brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs, or to require PMAs, FDA should rescind any existing "substantial equivalence" orders for such kits (specifically, the orders for the BEBIG and IBt kits, to the extent that they use bone wax or reformulated "faux bone wax" needle plugs). As a matter of course, particularly given the associated safety issues, FDA should also remove from the market any such kits without 510(k) clearance or PMA approval.

FDA has the authority to rescind "substantial equivalence" orders (*i.e.*, 510(k) clearances) in cases that involve: (1) a serious adverse risk to health and human safety, (2) data integrity or fraud, or (3) other compelling circumstances.[65] To the extent that the IBt or BEBIG brachytherapy kits use bone wax or reformulated "faux bone wax" needle plugs, we believe that all of these elements could be implicated, although just one of these grounds would be sufficient for rescission.

First, and most importantly, as detailed in Section C(1)(b) herein, we believe overwhelming scientific data indicates that "bone wax" plugs present serious adverse risks to health and human safety. Because the bone wax plugs do not absorb into the body, they could trigger the body's defense system, acting as a catalyst for many complications, including chronic inflammation

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[63] IBt Interstrand Advertising (Att. 44).

[64] *See* BEBIG Brachytherapy Kit, 510(k) No. K040339, Apr. 8, 2004 (Att. 45).

[65] *See* 66 Fed. Reg. 3523, 3524 (Jan 16, 2001).

(granulomatis infection), marked foreign body reaction, sarcomas (e.g., angiosarcomas), epistaxis, allergic reactions, sigmoid sinus thrombosis, foreign body venous embolization, and it could even contribute to quadriplegia.[66] In addition, the bone wax plugs could migrate to the lungs where they could cause further complications.[67]

As mentioned, we believe reformulated "faux bone wax" presents even greater adverse risks to health and human safety than bone wax. Reformulated "faux bone wax" can cause the same complications as traditional bone wax because it cannot absorb into the body. Moreover, given that reformulated "faux bone wax," to our knowledge, does not have a history of use in the body for any purpose, it could cause additional injuries.[68]

Second, addressing the third element, other compelling circumstances are present. As detailed in Section C(1)(b) herein, assuming that the BEBIG and IBt brachytherapy kits use bone wax or reformulated "faux bone wax" needle plugs, the kits present dramatically different issues of safety than the predicate brachytherapy kits, which either obviate the need for plugs through needle design or use plugs made of bioabsorbable synthetic suture material. Accordingly, they are not "substantially equivalent" to the predicate brachytherapy kits – and the "substantial equivalence" orders, in our view, should not have been issued in the first place.

Finally, addressing the second element, although we have not seen the actual 510(k) submissions and therefore are not in a position to know for certain, there may be reason for one to question the integrity of the data submitted to FDA in the 510(k)s submitted for the brachytherapy kits by IBt and BEBIG. Assuming that both BEBIG and IBt are in fact using needle plugs, FDA should revisit the data that the companies submitted in their 510(k) applications to determine whether the type of plug was disclosed.

Accordingly, assuming that IBt and BEBIG are using off-label bone wax or reformulated "faux bone wax" plugs in their brachytherapy kits, FDA has more than sufficient grounds to rescind the "substantial equivalence" orders, and it should do so immediately. Given the safety issues associated with bone wax and reformulated "faux bone wax" and the problems with showing "substantial equivalence," FDA should also act immediately to rescind any other "substantial equivalence" orders that have been issued for commercial brachytherapy kits using bone wax or reformulated "faux bone wax" needle plugs, to the extent that there are any.

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[66] *See supra*, discussion at Section C(1)(b) herein.

[67] *See supra*, discussion at Section C(1)(b) herein.

[68] *See supra*, discussion at Section C(1)(b) herein.

D. Environmental Impact

Nothing requested in this petition will have an impact on the environment, and thus, this petition should be categorically excluded from any applicable requirements in 21 C.F.R. pt. 25, subpt. C (2003) and 21 C.F.R. § 25.40 (2003).

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

* * * *

For the reasons listed herein, FDA should immediately take action to ban the sale of commercial brachytherapy kits that use bone wax or reformulated "faux bone wax" needle plugs. In the alternative, FDA should immediately require manufacturers of such devices to obtain PMA approval for their kits, rather than 510(k) clearance. In addition, FDA should rescind any existing 510(k) clearances for such products. It is imperative that FDA exercise its authority over these devices to protect brachytherapy patients from the potential safety issues associated with bone wax and reformulated "faux bone wax" needle plugs.

Very truly yours,

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