UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP., MERCK SHARP & DOHME B.V., AND ORGANON USA, INC.
Petitioners

v.

MICROSPHERIX LLC
Patent Owner

CASE NO: _____
U.S. PATENT: 6,514,193

PETITION FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

Merck Sharp & Dohme Corp., Merck Sharp & Dohme B.V., and Organon USA, Inc. ("Petitioners" or "Merck") request *inter partes* review ("IPR") and cancellation of claims 1-2 of U.S. Patent No. 6,514,193 ("the '193 Patent") (Ex. 1001). Microspherix LLC ("Microspherix") owns the '193 Patent, which claims a method of administering a drug by implanting a brachytherapy seed containing the drug and a radiopaque marker into the patient's body. This method is both anticipated and rendered obvious by the prior art.[1]

II. GROUNDS FOR STANDING

Petitioners certify that the '193 Patent is available for review under 35 U.S.C. § 311(c) and that it is not estopped from requesting an IPR challenging claims 1-2 on the grounds identified in this Petition.

III. PROPOSED GROUNDS OF UNPATENTABILITY

The present Petition details how the cited prior art anticipates and renders obvious each element of the challenged claims of the '193 Patent.

A. Prior Art Offered for the Present Unpatentability Challenges

This Petition states an anticipation ground under 35 U.S.C. § 102 in light of U.S. Patent No. 6,197,324 to Crittenden, filed July 15, 1998 and further claiming

[1] Mandatory notices under 37 C.F.R. § 42.8 can be found at the end of the Petition.

priority to application 08/993,586 filed December 18, 1997, and issued March 6, 2001 (Ex. 1008) both alone and further in view of the teachings of U.S. Patent No. 5,629,008, filed June 7, 1994 and issued May 13, 1997 (Ex. 1009) which Crittenden incorporates by reference into its specification. Crittenden is prior art under at least pre-AIA 35 U.S.C. § 102(e). To the extent Crittenden is not anticipatory, this Petition further states an obviousness ground based on Crittenden alone and in view of the '008 Patent.

In addition, this Petition states obviousness grounds under 35 U.S.C. § 103 using the following prior art:

- U.S. Patent No. 6,575,888 to Zamora (Ex. 1003) ("Zamora"), filed January 24, 2001, claiming priority to U.S. Provisional Patent App. No. 60/178,083 (filed Jan. 25, 2000) ("'083 PA") (Ex. 1027), is prior art under pre-AIA 35 U.S.C. § 102(e).
- U.S. Patent No. 5,938,583 to Grimm (Ex. 1004) ("Grimm"), filed December 29, 1997 and issued August 17, 1999, is prior art under pre-AIA 35 U.S.C. § 102(b).
- U.S. Patent No. 5,150,718 to De Nijs (Ex. 1005) ("De Nijs"), filed on February 14, 1992 and issued September 29, 1992, is prior art under pre-AIA 35 U.S.C. § 102(b).
- U.S. Patent No. 4,012,497 to Schopflin (Ex. 1006) ("Schopflin"), filed

September 23, 1975 and issued March 15, 1977, is prior art under pre-AIA 35 U.S.C. § 102(b).

- L. Mascarenhas, *Insertion and Removal of Implanon®*, Contraception 58:79S-83S (1998) (Ex. 1007) ("Mascarenhas 1998"), printed in December 1998 and publicly available no later than March 4, 1999 (*see* Hall-Ellis Decl. (Ex. 1010) ¶¶ 19-22 and Ex. 1007 at cover page), is prior art under pre-AIA 35 U.S.C. § 102(b).

B. Statutory Grounds for Challenge

The following grounds are raised against the challenged claims:

- Ground 1: Crittenden anticipates claims 1-2 under § 102(e).
- Ground 2: Crittenden alone and in combination with the '008 Patent renders obvious claims 1-2 under § 103(a).
- Ground 3: Zamora in view of Grimm render claims 1-2 obvious under § 103(a);
- Ground 4: De Nijs in view of Schopflin and Mascarenhas 1998 render claim 1 obvious under § 103(a);

IV. BACKGROUND

A. Description of the '193 Patent

The '193 Patent is a member of a family of patents owned by Microspherix

relating to implantable devices referred to in that patent as "brachytherapy seeds."[2] The '193 Patent states that "[r]adioactive seed therapy, commonly referred to as brachytherapy, is an established technique for treating various medical conditions, most notably prostate cancer." '193 Patent at 1:21-23. These seeds "are localized near the diseased tissue, [and] the radiation they emit is thereby concentrated on the cancerous cells and not on distantly located healthy tissue." *Id.* at 1:28-30. "The capsule is sized to fit down the bore of one of the needles used in the implantation device." *Id.* at 2:5-6; 6:12-34 (describing "conventional brachytherapy strand applicators").

The '193 Patent purports to improve upon the prior art by providing brachytherapy seeds where "[a] drug or other therapeutically active substance or diagnostic can be included in the strand in addition to, or as an alternative to, a radioisotope." *Id.* at 2:60-62. The claims of the '193 Patent are directed to a method of administering an implantable "brachytherapy seed" containing a "therapeutically active component comprising a non-radioactive drug." Unlike the claims in some related patents, the "brachytherapy seed" in claim 1 and the other challenged claims does not preclude the inclusion of a radioisotope in addition to

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[2] Petitioners have filed IPR petitions for three related patents: IPR2018-00393, -00402 and -00602.

the recited elements. *Cf.* '402 Patent (Ex. 1028) at cl. 1 ("wherein the strand is *non-radioactive* and does *not* contain a radioisotope").

The '193 Patent claims "method[s] of administering" the brachytherapy seeds via a "brachytherapy implantation needle." '193 Patent at Abstract. However, it does not purport to improve on prior art implantation devices—on the contrary, the '193 Patent states that its seeds are designed to be implanted "with the needles used in many conventional brachytherapy strand implantation devices." *Id.* at 6:12-13; *id.* at 15:49-55. A number of suitable implantation devices are described in, e.g., U.S. Pat. Nos. 2,269,963; 4,402,308 (Ex. 1018); 5,860,909; and 6,007,474 (Ex. 1017). *Id.* at 1:34-38.

B. Prior Art and the State of the Art

Brachytherapy, the therapeutic administration of radioactive implants, was an "established technique for treating various medical conditions, most notably prostate cancer" in the prior art. '193 Patent at 1:21-23; Langer Decl. ¶ 24; WO 97/19706 A1 (Ex. 1020) at 3:3-5. Needle instruments, which the '193 Patent refers to as "conventional brachytherapy seed applicators," were known in the art and used to place such implants into a particular diseased tissue, such as a malignant tumor in the prostate. Langer Decl. (Ex. 1002), ¶ 25; '193 Patent at 6:20-34; U.S. Patent No. 6,027,446 (Ex. 1014) at Fig. 1.

Brachytherapy implants have long been used to deliver therapeutic agents at

the site of a particular target tissue, reducing the toxicity associated with general systemic administration. Langer Decl., ¶ 25-27; U.S. Patent No. 6,030,333 (Ex. 1015) at 5:28-32. Sometimes the therapeutic agent would be paired with a radioisotope, but the prior art also taught implants that did not contain a radioisotope. Langer Decl., ¶ 28; Brem (Ex. 1011) at 1:33-37. In addition, many types of non-radioactive drug-eluting implants were known and used outside of brachytherapy to deliver a variety of therapeutic agents, including hormones for birth control, antibiotics, and other compounds. Langer Decl., ¶ 27, 29-31; U.S. Patent No. 5,871,437 (Ex. 1012) at 3:14-32. The addition of a radiopaque material, such as barium sulfate, to such implants was also known. Langer Decl., ¶ 34; U.S. Patent No. 6,030,333 at 8:3-4; U.S. Patent No. 6,080,099 (Ex. 1016) at 1:32-34; GB 2,168,257 (Ex. 1019) at 1:86-88. This had the benefit of making them X-ray visible to aid in their implantation and removal. Langer Decl., ¶ 35; U.S. Patent No. 6,007,475 (Ex. 1013) at 1:34-36.

Dash 1998 (Ex. 1021), an article published in the Journal of Pharmacological and Toxicological Methods in 1998, provides an overview of some implantable drug delivery systems known in the prior art, which were known to take a variety of forms. Langer Decl., ¶ 32. For example, Dash 1998 discloses rod-shaped implants, such as that disclosed in Figure 3 and Norplant®, a product comprising multiple flexible rod-shaped implants of 36-40 mm in length that elute

a hormone drug to produce a contraceptive effect. Dash 1998 at 4; *see also* Thomsen 1985 (Ex. 1022) at 224, Figs. 1-2; Segal 1983 (Ex. 1023) at 161-62; Langer Decl., ¶ 32.

Langer 1981 (Ex. 1024) and Langer 1990 (Ex. 1026) are journal articles published in 1981 and 1990, respectively, that provide an overview of drug release mechanisms from polymer implants known in the prior art. Langer Decl., ¶ 33. These references teach that "[t]he most common release mechanism is diffusion" through the polymer surrounding the drug. Langer 1990 at 1529 (Figs. 1A-B); Langer 1981 at 202; Langer Decl., ¶ 33. Both references describe "reservoir systems" in the prior art where a drug in the core of the implant diffuses through a polymer wall surrounding the core, as shown in Langer 1981, Figure 1 reproduced below.

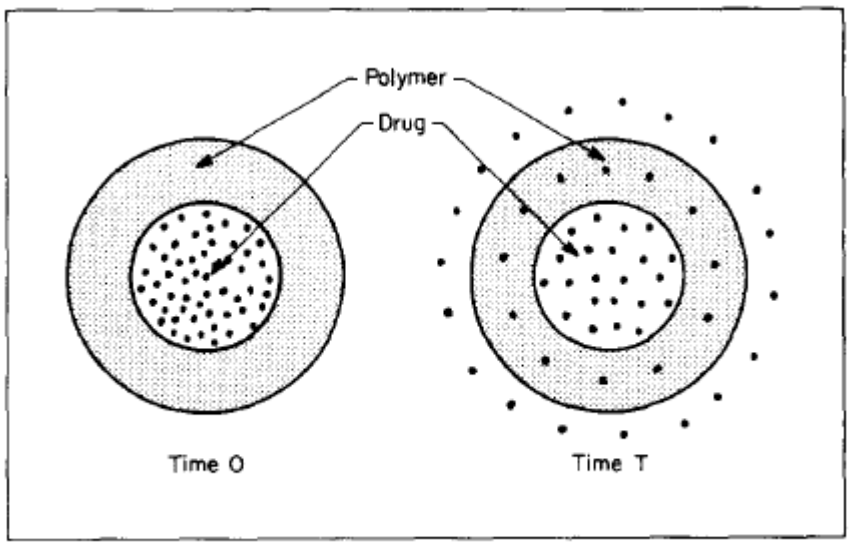

Figure 1 Idealized diffusion-controlled reservoir release system

See also Langer 1990 at 1529 (describing various "reservoir system" implants,

including Norplant®).

The references in the grounds raised in this Petition illustrate these teachings. As discussed below, Zamora, like the '193 Patent, is directed to biocompatible non-metal implants used to deliver locally a therapeutic agent to treat cancer. Such implants were part of the broader range of non-metal implants known in the prior art, a survey of which is provided in Dash 1998, as discussed above. Langer Decl., ¶ 32, 35. De Nijs and Schopflin are directed to implants for the systemic delivery of a contraceptive hormone, to produce a contraceptive effect. Microspherix has taken the position that the '193 Patent claims are not limited to brachytherapy or localized drug delivery and encompass contraceptive implants similar to that taught in De Nijs. Amended Complaint (Ex. 1025), ¶¶ 47, 57, 121-81. Giving the challenged claims their broadest reasonable interpretation,[3] these references are relevant prior art demonstrating the unpatentability of the '193 Patent claims.

1. Crittenden

Crittenden teaches "systems and methods for implanting a depot into a tissue

[3] Petitioners note that a different, narrower claim construction standard governs in infringement litigation and reserve all rights regarding appropriate claim constructions under the same.

wall to thereby deliver a therapeutic agent selected for the condition being treated." Crittenden at 3:19-22. In one embodiment, "a solid pellet is formed from a biodegradable polymer that has been doped or 'seeded' with the desired therapeutic agent." *Id.* at 9:54-56. Crittenden teaches that "[t]he therapeutic agent can be any compound that is biologically active and suitable for long term administration to a tissue or organ." *Id.* at 9:43-45. "To aid in visualizing the implant by fluoroscopy[4] or x-ray, a sphere of previous metal, such as gold or platinum, can be covered with the drug-filled polymer." *Id.* at 9:61-64. Such a configuration of drug-filled polymer surrounding a radiopaque core is picture below in Figure 4A:

[4] Fluoroscopy is a type of x-ray in which a fluoroscope is used to render the x-ray image visible on a screen in real time. *See* Langer Decl., ¶ 55; Black's Medical Dictionary (Ex. 1043) at 209.

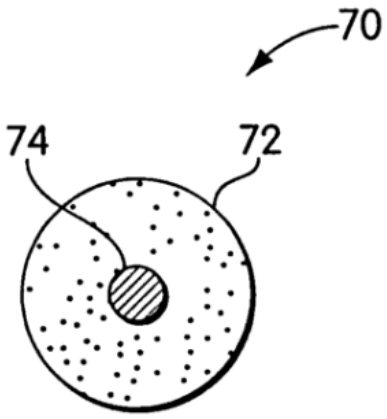

Fig. 4A

Crittenden explains that this spherical pellet is just one example and that "[i]t will be apparent to one of ordinary skill in the art that other drug delivery implants can be employed with the systems described herein, including … cylindrical implants that incorporate a solid, drug-filled polymer core with the container-type biodegradable polymer wall." *Id.* at 10:24-29. As an example of such implants, Crittenden points to and incorporates by reference the '008 Patent, which teaches a cylindrical container-type implant as shown in Figure 1 below. *See, e.g.*, '008 Patent, Fig. 1 (shown below).

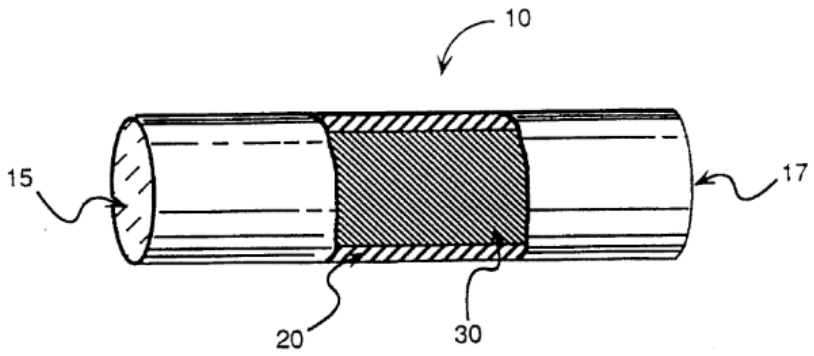

Fig. 1

Crittenden teaches that "[a] radio-opaque metal core could be incorporated into this 'container' type pellet to facilitate viewing" on x-ray. Crittenden at 10:6-8.

Crittenden additionally teaches an apparatus and method for inserting these "pellets" that includes a "needle-like" "delivery chamber" that "can be about 0.010 to 0.050 inches in diameter." *Id.* at 8:50-61. "The physician can preload the delivery chamber 14 with the set of pellets that have been selected to deliver the proper depot of therapeutic agent to the tissue." *Id.* at 10:66-11:1; *see also id.* Fig. 2A (depicting pellets introduced into delivery chamber).

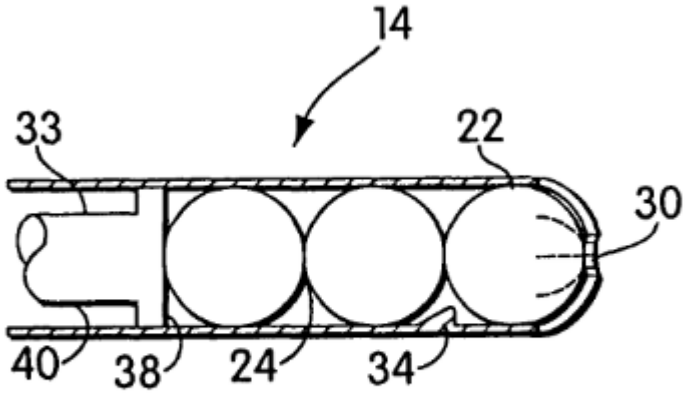

Fig. 2A

After using a catheter to locate the delivery chamber adjacent to the target tissue, "the physician drives the delivery chamber into the tissue and to the targeted area." *Id.* at 11:30-45. The physician subsequently "actuates the control mechanism and ejects a pellet from the delivery chamber, implanting the pellet within the targeted area." *Id.*

2. Zamora

Zamora teaches "[a] bioabsorbable brachytherapy device" that includes a "tubular housing [] made from biocompatible and bioabsorbable polymeric material" that "enclose[s] [a] radioactive material." Zamora (Ex. 1003) at Abstract. This implantable device "may further include a radiopaque medium and one or more therapeutic drugs." *Id.* "The invention thus provides methods and devices for the delivery of localized radioactivity, and preferably also concurrent delivery of localized chemotherapeutic, bioactive or other drugs to patients for therapeutic purposes." *Id.* at 5:19-23.

Figure 7 is representative:

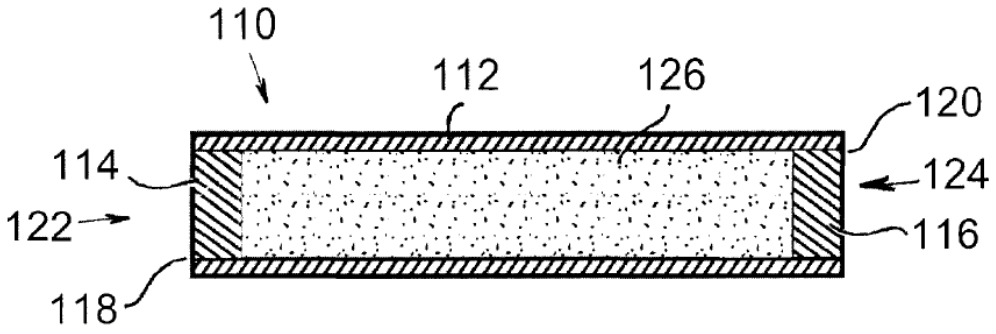

FIG. 7

Id. at Fig. 7. "The housing comprising tube 112 and plugs 114 and 116 are made from a suitable bioabsorbable and biocompatible polymer." *Id.* at 8:1-4.

"The tube 112 is then filled with a complex 126 that includes the radioisotope." *Id.* at 7:63-64. The complex may comprise a "matrix" onto which

the radioisotope is chelated, and such complex may be a "polymer" that "can be plasma coated and then subsequently conjugated to the chelates." *Id.* at 11:15-19. Additionally, "a therapeutic drug … may be disposed within at least a portion of the structure of the bioabsorbable polymeric … tube." *Id.* at 4:46-51.

Because the housing is made from polymeric materials, it "is relatively transparent to X-rays" and is "not sufficient to permit easy visualization." *Id.* at 12:25-28. Zamora teaches that "[t]his may be overcome by the use of a radiopaque medium," which Zamora describes as "a biocompatible radiopaque material capable of being detected by X-rays and conventional radiographic methods, and optionally by magnetic resonance imaging and ultrasound imaging." *Id.* at 12:28-29, 7:23-26. In one embodiment, "a barium-based radiopaque agent is admixed with the other constituent elements forming complex 126." *Id.* at 12:33-35. In another, the radiopaque agent "forms a part of a coating over the device 110." *Id.* at 12:35-37.

"The brachytherapy devices are then implanted in a patient in a conventional manner, using methods substantially similar to those employed for treatment utilizing metal brachytherapy sources." *Id.* at 13:46-49.

a) Zamora is Prior Art

In recent responses to other petitions, Patent Owner argues that Zamora is not prior art because it is not entitled to the benefit of its provisional application.

That argument is a reversal of the position Patent Owner has taken for over 14 years in the prosecution of the Microspherix patent family.

While it was not cited during prosecution of the '193 Patent, Zamora has repeatedly been the basis for rejecting Patent Owner's related applications. At no time did Patent Owner ever contest that Zamora is, in fact, prior art as of the date of its provisional application. Indeed, Patent Owner repeatedly classified Zamora as prior art in its responses both to the examiner and the Board. '326 App., 10/20/03 Remarks (Ex. 1040) at 20-21; '793 App., 5/16/08 Remarks (Ex. 1045) at 7; '793 App, 12/24/08 Remarks (Ex. 1050) at 6, 8; '793 App., 3/2/09 Remarks (Ex. 1046) at 9, 11; '793 App., 3/9/09 Remarks (Ex. 1047) at 9, 12; '793 App., 1/28/10 Remarks (Ex. 1048) at 16, 18; '618 App, 5/26/15 Appeal Br. (Ex. 1049) at 7-8, 12; '159 App., 2/15/17 Remarks (Ex. 1051) at 10. These concessions bind Patent Owner here. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003); *Constant v. Adv. Micro-Devices Inc.*, 848 F.2d 1560, 1569-70 (Fed. Cir. 1988); *In re Nomiya*, 509 F.2d 566, 571 n.5 (C.C.P.A. 1975)).

Patent Owner contends its prior statements and acquiescence that Zamora is prior art does not bind it now, citing a series of inapposite cases. *See Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1340 (Fed. Cir. 2010); *Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1286 (Fed. Cir. 2012); *Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 874 (Fed. Cir. 1991). In

those cases, the applicant successfully traversed a rejection based on certain limitation(s), while remaining silent on others. The Court held that the applicant's silence was not an admission that the other limitations were met. But here the applicant was not silent, rather Patent Owner has affirmatively characterized Zamora as prior art for more than a decade. Nor is this an instance where the applicant successfully traversed the rejection on one ground, while remaining silent on another. Here, Patent Owner *failed* to overcome rejections based on Zamora, even on appeal to the Board. *See* '407 App., 4/30/12 Board Decision (Ex. 1038) at 1. Since Zamora's status as prior art was condition precedent to those other rejections, Patent Owner was not merely silent, but rather affirmatively conceded the point in those prior proceedings.

Moreover, it is beyond dispute that Zamora is, in fact, entitled to the benefit of its provisional filing date. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1381 (Fed. Cir. 2015). Section 119 has only four requirements for Zamora to be entitled to its provisional date; all of which are present. The statute requires that the invention (*i.e.*, as claimed) be (1) "disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application" (2) "by an inventor or inventors named in the provisional application" (3) in an application filed "no[] later than 12 months after the date on which the provisional application was filed" (4) with "a specific reference to the provisional

application." 35 U.S.C. § 119(e)(1) (2006). At no point in the prosecution history or in the related IPRs has Patent Owner ever contested that any of these statutory requirements are missing. Nor could it. Zamora (Ex. 1003) at [22], [60], [75] (filing dates, specific reference, inventors), 1:6-10 (specific reference); '083 PA at 1 (filing date, inventors).

As for section 112 support, the Federal Circuit in *Dynamic Drinkware* concluded that the proper priority inquiry is whether "the disclosure of the provisional application provide[s] support for the *claims* in the reference patent." 800 F.3d at 1377, 1381. Accordingly, as shown below for representative claims 1 and 9, Zamora's claims are supported by the written description of the '083 PA, and thus Zamora is entitled the benefit of its provisional filing date.

Zamora Claim 1	**Supporting Description**
A brachytherapy device for use in radiation treatment of an affected tissue region, the brachytherapy device comprising:	'083 PA 5:12-14.
A radioactive material comprising a radioisotope;	'083 PA 5:16-25; 5:28-30; 6:30-31; 8:9-11; Fig. 2.
a bioabsorbable polymeric housing containing the radioactive material,	'083 PA 6:21-26; 6:32-7:6; Fig. 2.

the housing being formed by at least one tube having an axis and two ends, the at least one tube being sealed at each end; and	’083 PA 7:8-13; 7:26-27; Fig. 2.
a radiopaque medium,	’083 PA 8:13-17.
wherein the radiopaque medium is disposed either on at least a portion of an external surface of the tube, within at least portion of a structure of the tube, or within the radioactive material;	’083 PA 8:13-17.
wherein there is no metal layer between the radioactive material and the bioabsorbable polymeric housing.	’083 PA Fig. 2; Fig. 3i; 6:15-18.
Zamora Claim 9	
The device of claims 1, 2, 4, or 6, further comprising an effective amount of a therapeutic drug disposed on at least a portion of the external surface of the tube.	’083 PA 11:9-15; Figs. 3d-g.

Patent Owner has not disputed that the '083 PA meets all of the requirements of Section 119. Instead, it has argued that, in addition to meeting the statutory requirements, all of the portions of Zamora cited in petition must have been "carried forward" from the '083 PA. That argument fails to show that Zamora is not prior art against the '193 Patent for several reasons.

First, it is not the law. The Federal Circuit in *Dynamic Drinkware* considered a Board decision addressing whether relied-on subject matter in a prior art patent must also be "present in and supported by its provisional," and held that the proper inquiry is whether "the disclosure of the provisional application provide[s] support for the claims in the reference patent." 800 F.3d at 1377, 1381. The Federal Circuit chose not to follow the reasoning of the Board, and addressed the cases upon which it relied—the same cases cited here by Patent Owner (and the panel in *Ariosa v. Illumina*, IPR2014-01093, Paper 69 (P.T.A.B. Jan. 7, 2016)); 800 F.3d at 1377, 1380-81 (citing *In re Giacomini*, 612 F.3d 1380 (Fed. Cir. 2010) and *Ex parte Yamaguchi*, 88 U.S.P.Q.2d 1606 (B.P.A.I. 2008)).

Confirming that the invention as claimed is the proper focus, the Federal Circuit noted that *Giacomini* addressed whether the provisional "provide[d] written description support for the claimed subject matter," which, in that case, was waived. 800 F.3d at 1380-81. Thus, contrary to Patent Owner's argument, the

"carried forward" language in *Giacomini* concerned whether the "invention" (*i.e.*, the claim) was "carried forward" from an earlier application. 612 F.3d at 1383. Similarly, *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH* addressed support for claims of related patents as well, but not for determining prior art priority. 237 F.3d 1359, 1367 (Fed. Cir. 2001).

Patent Owner's reliance on *Application of Klesper*, 397 F.2d 882 (C.C.P.A. 1968) and *Application of Lund*, 376 F.2d 982, 988 (C.C.P.A. 1967), both of which predate the enactment of § 119(e) and the advent of provisional applications by 27 years, is equally fruitless. In *Klesper*, the court upheld the prior art reference as adequately supported by its provisional, demanding less detail for those limitations that did not constitute the applicant's "contribution to the art." 397 F.2d at 887. *Lund* addresses a completely different question (whether material *included* in an abandoned parent application but *not included* in the prior art reference in question could be considered part of the disclosure) and is therefore inapposite. 376 F.2d at 988.

Second, even if it were the law, the pertinent description in Zamora is, in fact, carried forward from its provisional application as demonstrated by the

parallel citations to the ’083 PA in the analysis of Zamora in Ground 3 below.[5] *See infra* at Section VII.C.

3. Grimm

Grimm teaches a device and method for “radioactive seed implant treatment for prostate cancer” using a “needle combination for implanting such seeds into the prostate.” Grimm at 1:7-10. Grimm teaches that “transperineal seed implantation,” “known as brachytherapy,” “is advantageous in that it can be performed on an outpatient basis, permitting the patient to resume normal activities in just a few days.” *Id.* at 1:46-53.

In the method disclosed in Grimm, “a solid, small diameter (typically 19 gauge) surgical stainless steel insertion stylet 22” is positioned in the prostate (33). *Id.* at 3:54-57. A “hollow sleeve 28 is inserted over the insertion stylet 22 into the prostate,” as shown in Figure 3B, after which “[i]nsertion stylet 22 is withdrawn from sleeve 28, leaving just sleeve 28 in place.” *Id.* at 4:2-4, 4:22-23.

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[5] In addition, because the only Microspherix application that predates Zamora’s utility application is provisional application 60/249,128, Patent Owner also has to prove that the challenged ’193 Patent claims are entitled to the benefit of that provisional—which they are not.

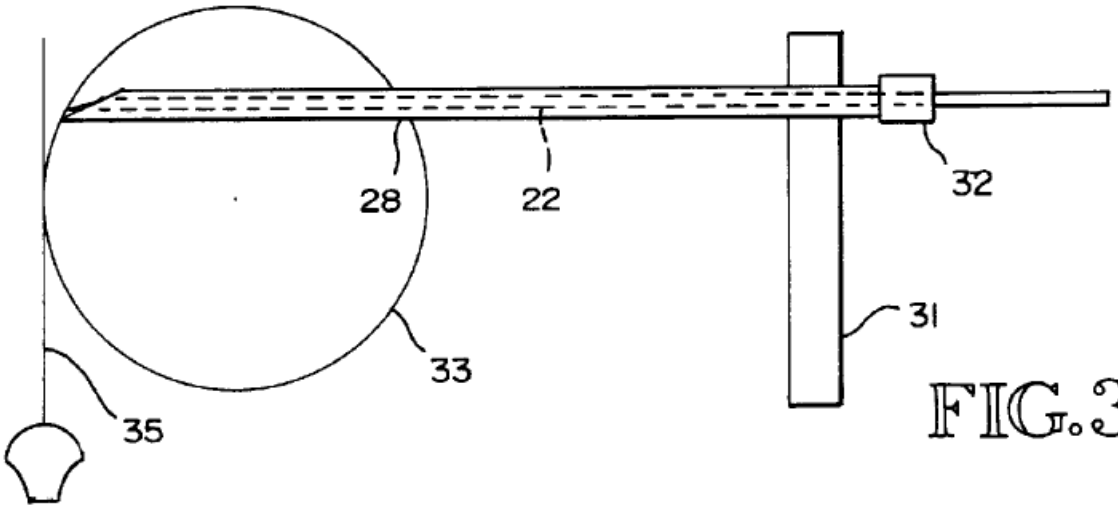
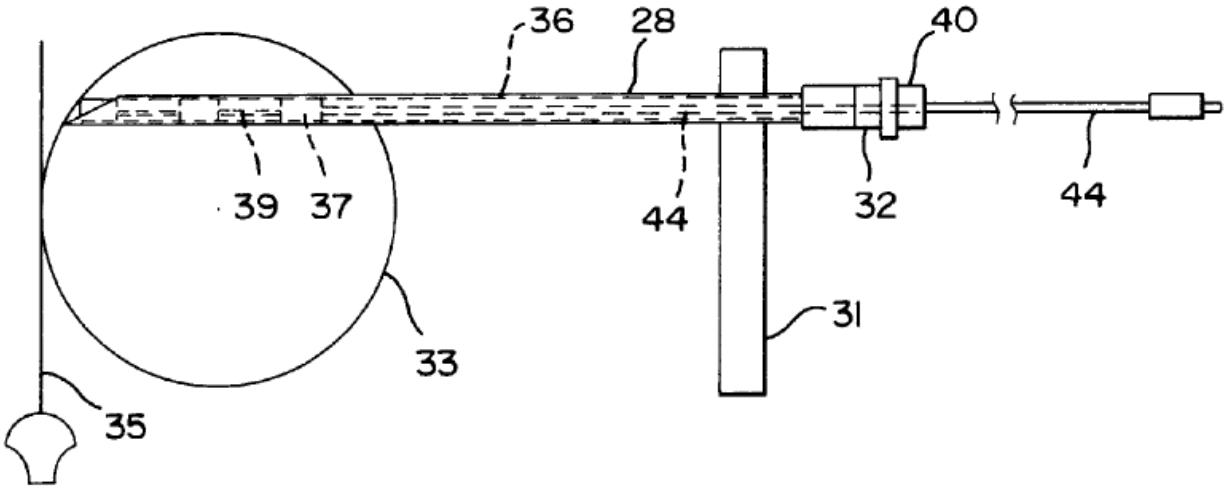


FIG. 3B

"The needle portion 36 of the needle combination … is loaded … with successive radioactive seeds." *Id.* at 4:14-16. Needle portion 36, "which is approximately the same diameter as the insertion stylet 22," is then inserted through sleeve 28 into the prostate as shown in Figure 3D. *Id.* at 4:23-25. An "implant stylet 44" is inserted into the proximal end of needle portion 36, resting against the brachytherapy seeds. *Id.* at 4:25-27.

FIG.3D



"At this point, implant stylet 44 is held in position by the operator while needle 36 and sleeve 28 together are slowly withdrawn, leaving a line of seeds … along the line vacated by the withdrawing needle/sleeve." *Id.* at 4:41-45, Fig. 3E.

4. De Nijs

De Nijs teaches "an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally." De Nijs (Ex. 1005) at Abstract. The implant comprises a "cylindrical or virtually cylindrical" rod "with a maximum section of about 2 mm" and a "variable length" that is "preferably between 1 and 4 cm." *Id.* at 1:62-67. The "core material" of the rod contains an "ethylene/vinyl acetate copolymer," (or "EVA") that "functions as a matrix for 3-keto-desogestrel, levonorgestrel or gestodene as active contraceptive substances," which are hormones. *Id.* at 2:3-10. The

"polymer loaded with active substance is encased by a polymer membrane." *Id.* at 1:43-44. The implant is shaped such that "it can be fitted subcutaneously with an ordinary hypodermic needle." *Id.* at 1:11-13.

5. Schopflin

Schopflin teaches a "sustained release pharmaceutical composition[] containing one or more nonionic, lipophilic drugs," and a "low temperature vulcanizable (LTV) silicone elastomer" polymer. Schopflin (Ex. 1006) at Abstract. Schopflin further discloses that "[f]or improved X-ray localization in the body, the active agent carrier can contain a radiopaque amount of barium sulfate." *Id.* at 7:41-43.

The polymers Schopflin teaches "are known to be suitable carrier materials for depot drug preparations providing long-term treatment in a living organism, since they are neither degraded nor resorbed by the organism and show a good tissue compatibility as compared to other synthetic polymers." *Id.* at 1:21-26. The "suitable drugs with which, in a novel, effective manner, undesired conditions in or at the human or animal organism are to be treated or controlled and which exhibit these properties include but are not limited to hormones." *Id.* at 5:63-67.

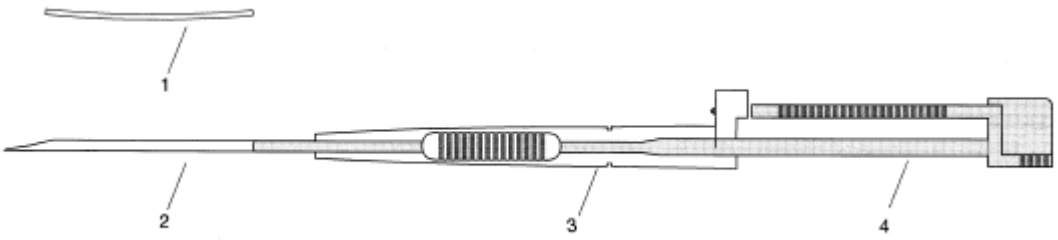
Schopflin teaches that the shape of its implants "can be arbitrarily selected" and "[t]hus, the desired form can be determined only by the type and amount of the medicinal agent to be administered, the desired drug release rate from the carrier

and the location of administration." *Id.* at 6:53-62. In one embodiment, Schopflin teaches that it is "possible to make the medicinal agents of a core containing the drug and of an outer silicone elastomer shell casing with a low drug content and having any desired layer thickness." *Id.* at 7:1-4. In another, the hormone, polymer, and radiopaque material are first blended and subsequently shaped into "cylinders having a length of 20 mm[] with a diameter of 1.5 mm." *Id.* at 9:5-20.

6. Mascarenhas 1998

Mascarenhas 1998 is an article titled "Insertion and Removal of Implanon®," published in the journal Contraception in 1998. It discloses the applicator for Implanon®, a 4 cm x 2 mm polymer implant containing etonogestrel, a contraceptive hormone[6]. Mascarenhas 1998 at S79. Mascarenhas 1998 describes the implantation device "sterile, disposable applicator" comprising a "plastic body," "obturator," "cannula," and a "needle" that is "preloaded with an Implanon rod … for insertion," as shown below. *Id.* at S79-80, Fig. 1; *see also* U.S. Patent No. 5,279,555 Fig. 1.

[6] The dimensions and construction of Implanon® are identical to those described as a preferred embodiment of De Nijs. *Compare* Mascarenhas 1998 at S79 *with* De Nijs at 1:62-2:29.



1 Implanon rod
2 Needle
3 Plastic body
2+3 Cannula
4 Obturator

Figure 1. Implanon applicator.

During implantation, the "needle is introduced directly under the skin" on "the inside of the nondominant upper-arm." *Id.* at S79. The obturator (4) rests inside the proximal end of the cannula (3) and against the Implanon rod (1), as shown above. To actuate, the "obturator is turned 90°," and the "cannula is slowly pulled out of the arm while keeping the obturator tightly fixed in place." *Id.* The obturator holds the Implanon rod in place as the cannula is retracted along the obturator, leaving the implant in place under the skin as the needle is withdrawn. *Id.*

C. Prosecution History

The '193 Patent issued without rejection. Although not cited during the '193 Patent prosecution, some prior art raised in this petition was specifically addressed in related applications. Patent Owner's statements in prosecution of a "familial patent relating to the same subject matter" are highly relevant. *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314-16 (Fed. Cir. 2007). Patent Owner has

argued in a related proceeding that this history is irrelevant to the present proceeding, citing *Mexichem Amancho Holdings S.A. de C.V. v. Honeywell Int'l, Inc.*, IPR2015-01309, Paper 11 (P.T.A.B. Jan. 6, 2016). But in *Mexichem*, the Petitioner had advanced a ground "without citations to supporting evidence or testimony" in its petition, and the Board declined to rely exclusively on findings from other proceedings. *Id.* at *4. Here, however, the Petition sets forth evidence, which the prosecution history of Patent Owner's related applications confirms is credible and relevant to the invalidity of the challenged claims.

Zamora. The Board addressed Zamora on appeal from the Examiner's final rejection of claims in a related application, No. 10/854,407, fully affirming the rejection of Microspherix's claims as obvious in light of Zamora and other references. '407 App., 4/30/12 Board Decision at 1. The claims at issue in that appeal were directed to a brachytherapy seed that, *inter alia*, was: (a) "radiopaque," (b) composed of a "biodegradable polymer[]," (c) "cylindrical shap[ed] with a diameter of at least 0.5 millimeters," and (d) contained "a therapeutically effective amount of a therapeutic agent dispersed within the polymer." *Id.* at 3. The Board held that Zamora teaches each of those limitations.

Id. at 5-8.[7]

As explained above, while the claims of the '193 Patent recite a brachytherapy seed "comprising," *inter alia*, a "non-radioactive drug," they do not preclude the inclusion of a radioisotope in addition to that drug. In other words, the claims of the '193 Patent encompass brachytherapy seeds, like those taught in Zamora, which include both a non-radioactive drug and a radioisotope. Thus, Microspherix's primary argument for distinguishing Zamora in other related applications, *i.e.*, that Zamora requires a radioisotope in addition to a therapeutic agent, is not a basis for distinguishing the claims that are the subject of this petition. *See* '470 App., 4/30/12 Board Decision at 4; '401 Patent, 10/14/16

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[7] During prosecution of other related applications, Microspherix characterized Zamora as follows: "Zamora describes a brachytherapy device containing a radioactive material … sealed in a bioabsorable polymeric housing. The device can also include a radiopaque medium, which may be disposed on at least a portion of the bioabsorbable polymeric housing, within at least a portion of the bioabsorbable housing, or within the radioactive material. In addition to containing a radioactive material, Zamora's device may optionally contain a therapeutic agent." '401 Patent, 10/14/16 Remarks at 7; '661 Patent, 10/20/03 Remarks at 14.

Remarks (Ex. 1041) at 8-9.

V. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") of the '193 Patent would typically have at least a Master's degree in biomedical engineering, chemical engineering, or a related field with several years of experience with biomedical implants and drug delivery systems. Langer Decl., ¶¶ 13-16.

VI. CLAIM CONSTRUCTION

Pursuant to 37 C.F.R. § 42.100(b), a claim in IPR is given the "broadest reasonable construction in light of the specification" ("BRI").[8] All claim terms not specifically addressed below, for the purposes of this IPR only, have been accorded their BRI. To the extent that the Board disagrees with any proposed construction, Petitioner submits that the claims are still unpatentable in light of the prior art raised by this Petition.

A. "Brachytherapy" and "Target Tissue"

In the related infringement litigation, Patent Owner alleges that the terms

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[8] Because this standard is different from and generally broader than the claim construction standard that applies in patent infringement litigation, Petitioners reserve the right to argue for a different construction under the narrower claim construction standard applicable there.

"brachytherapy seed," "brachytherapy implantation instrument," and "brachytherapy implantation instrument" (collectively the "brachytherapy" limitations) in claim 1 do not limit the claim to brachytherapy involving radioactive seeds. *See also* MTD Opp. (Ex. 1029) at 22-24. Rather, Patent Owner argues that "'[b]rachytherapy seed' and 'brachytherapy implantation device' are merely names for the objects used in the claimed methods." *Id.* Regarding the "target tissue" limitations, Patent Owner alleges that claim 1 "does not require the target tissue to be the same site of action as the therapeutic agent" and that the specification "contemplates delivery in a brachytherapy seed of both locally and systemically … acting drugs." MTD Opp. at 14-15. Patent Owner's position is further demonstrated by the allegations in its Amended Complaint, alleging that Merck's Nexplanon product—a non-radioactive contraceptive implant that is implanted in a subject's arm to produce a contraceptive effect in remote tissues, meets the "brachytherapy" and "target tissue" limitations and therefore infringes claim 1. *Id.* at 12; Amended Complaint ¶¶ 123-133, 156-69, 175-81.

For the limited purpose of this IPR where the claims are given their BRI, Petitioners apply Patent Owner's construction that the "brachytherapy" limitations do not limit claim 1 to radioactive seed therapy, nor do the "brachytherapy" and "target tissue" limitations require the target tissue at the site of implantation to be the same tissue targeted by therapeutically active component and non-radioactive

drug.

B. "Seed"

For the purpose of this IPR, Petitioners submit that the BRI of the term "seed" (recited in the challenged claims as a "brachytherapy seed") refers to an implant of any size or shape suitable for passing through a needle, including, *inter alia*, "spheroid," "conical" and "cylindrical" structures. '193 Patent at 6:35-42 ("Brachytherapy seeds within the invention … can be any shape suitable for passing through the bore of a needle.").

In response to other petitions, Patent Owner has argued that the term "seed" requires that the implant be flexible. *See* IP2018-00602, Paper 10 at 16-17; IPR2018-00402, Paper 8 at 16-17; IPR2018-00393, Paper 6 at 15-16. Petitioners dispute that construction as well as any argument from Patent Owner that the BRI of the term "seed" similarly requires the implant to be flexible. This is particularly so for the '193 Patent, which does not include the term "flexible" or "flexibility" in either the claims, or the specification.

VII. DETAILED EXPLANATION OF UNPATENTABILITY GROUNDS

A. Ground 1: Claims 1-2 are Invalid as Anticipated by Crittenden

1. Claim 1

a) "A method for administering a therapeutically active component to a target tissue in a subject, the method comprising the steps of"

Crittenden teaches this limitation. Langer Decl., ¶ 70. Crittenden teaches "methods for implanting a depot into a tissue wall to thereby deliver a therapeutic agent selected for the condition being treated." Crittenden at 3:19-22; *see also id.* at Abstract, 4:34-65,5:15-22, 5:51-64, 9:42-45, 10:46-11:45. These methods result in "local delivery of a therapeutic agent." *Id.* cl. 1.

b) "providing a brachytherapy seed comprising"

Crittenden teaches this limitation. Langer Decl., ¶ 71. Crittenden discloses seeds, including "cylindrical implants" with the same general dimensions as those recited in the '193 Patent at 6:12-20. Crittenden at 10:24-31 (incorporating by reference U.S. Patent No. 5,629,008); U.S. Patent No. 5,629,008 at Example II (cylindrical pellet of 10 x 3 mm). Crittenden also discloses spherical seeds, as contemplated by the '193 patent. *Compare* '193 Patent at 6:35-40 ("seeds within the invention can be … spheroid") *with* Crittenden at 9:46-48, Fig. 4A ("The pellets described above can be formed as mini-spheres that are on the order of about 0.005 inches to about 0.04 inches in diameter."). The '193 Patent teaches a brachytherapy seed in which "[a] drug or other therapeutically active substance can be included in the seed in addition to, or as an alternative to, a radioisotope." '193 Patent at 2:60-62. Because Crittenden teaches a seed that administers a therapeutically active agent, as explained above at Section VII.A.1.a), Crittenden teaches the provision of a brachytherapy seed. Langer Decl., ¶ 71.

c) "a non-metal biocompatible component"

Crittenden teaches this limitation. Langer Decl., ¶ 72. Crittenden teaches that the seeds may be "formed from a biodegradable polymer" which is "[t]ypically … a synthetic polymer, such as poly(lactic acid) or polyorthoesters." Crittenden at 9:52-67. Crittenden also describes "implants that incorporate a solid, drug-filled polymer core with the container-type biodegradable polymer wall." *Id.* at 10:24-30. These polymers are non-metal biocompatible components. Langer Decl., ¶ 72.

Crittenden incorporates by reference the implants taught in the '008 Patent, which are seeds with cylindrical containers constructed of "silicone … or other types of medical/surgical grade plastics" which "include, but are not limited to, polyethylene, polypropylene and parylene." '008 Patent at 3:21-27; Crittenden at 10:30-31. These seeds contain a "biodegradable matrix," which is "made of materials, usually polymers, which are degradable by enzymatic or acid/base hydrolysis." '008 Patent at 4:66-5:2; *see also id.* at 5:65-6:11, Examples I-XIV. These materials include non-metal biocompatible components. Langer Decl., ¶ 73.

d) "a therapeutically active component comprising a non-radioactive drug"

Crittenden teaches this limitation. Langer Decl., ¶ 74. Crittenden teaches a therapeutically active component comprising a non-radioactive drug, which can include "any agent capable of being locally delivered including, but not limited to,

pharmaceutical compositions or formulations." Crittenden at 3:34-44; *see also id.* at 9:42-45 ("The therapeutic agent can be any compound that is biologically active and suitable for long term administration to a tissue or organ."), 3:18-34 (describing agents including "angiogenesis compounds," "antiarrhythmic drugs" and "anesthetic agents). Crittenden also describes classes of "local anesthetic agents" that include, *inter alia*, "procaine" and "lidocaine." *Id.* at 12:56-13:27. Crittenden therefore teaches the inclusion of a therapeutically active component comprising a non-radioactive drug.

Further, the incorporated implants of the '008 Patent also comprise a therapeutically active component comprising a non-radioactive drug. Langer Decl., ¶ 75. The '008 Patent teaches that the "therapeutic agents [in its implants] can be any compound that is biologically active and requires long term administration to a tissue or organ for maximum efficacy." '008 Patent at 6:12-45; *see also id.* at 4:52-55; *see also id.* at 3:4-9, 5:28-29.

e) "a radiopaque marker"

Crittenden teaches this limitation. Langer Decl., ¶ 76. Crittenden teaches that its seeds may "include a radio-opaque marker typically located at the core of the pellet which facilitates the fluoroscopic viewing of the delivery of the pellets." Crittenden at 4:45-48. These markers "aid in visualizing the implant by fluoroscopy or x-ray" and may comprise "a sphere of a precious metal, such as

gold or platinum." *Id.* at 9:61-65; *see also id.* at 10:6-8. A POSA would recognize these materials as commonly used radiopaque materials. Langer Decl., ¶ 77. Indeed, the '193 Patent itself lists "gold" and "platinum" as examples of radiopaque markers. '193 Patent at 11:60. In addition, Crittenden teaches that "[a] radio-opaque metal core could be incorporated into" a "'container' type pellet," which would include the cylindrical container implants taught in the '008 Patent, "to facilitate viewing." Crittenden at 10:6-8.

f) "said biocompatible component being"

As explained above at Section VII.A.1.c), Crittenden discloses a biocompatible component.

g) "(a) physically associated with a therapeutically active component "

Crittenden teaches this limitation. Langer Decl., ¶ 79. As discussed above at Section VII.A.1.c), the matrix of Crittenden's seeds comprise a biocompatible component. Crittenden teaches that the "biodegradable polymer" of the seed is "doped or 'seeded' with the desired therapeutic agent." Crittenden at 9:54-56. Crittenden also teaches that "[o]ptionally, the pellets can carry a plurality of therapeutic agents, … by solidifying a plurality of agents within the polymer coating of each pellet." *Id.* at 10:51-53. Therefore, the biocompatible component is physically associated with a therapeutically active component.

The implants incorporated from the '008 Patent also disclose this limitation.

Specifically, the ’008 Patent describes seeds comprising cylindrical containers filled with a solid, drug-filled polymer core. ’008 Patent at 3:3-32, 5:23-30, Figs. 1-2. The polymer in the core of these seeds is a biocompatible component that is physically associated with a therapeutically active component, *i.e.*, the drug. *Id.* at 3:4-6, 4:52-65, 5:65-6:11; Langer Decl., ¶ 80.

h) “(b) in contact with said radiopaque marker”

Crittenden teaches this limitation. Langer Decl., ¶ 81. As discussed above at Section **Error! Reference source not found.**, Crittenden teaches that its radiopaque marker may be “at the core of the pellet,” which is coated with a non-metal biocompatible polymer. Crittenden at 4:45-48; *see also id.* at 9:61-65 (“[A] sphere of precious metal, such as gold or platinum, can be covered with the drug-filled polymer.”). The biocompatible component is therefore “in contact with” the radiopaque marker.

In addition, Crittenden incorporates by reference the cylindrical seeds taught in ’008 Patent and teaches that “[a] radio-opaque metal core could be incorporated into this ‘container’ type pellet to facilitate viewing.” Crittenden at 10:6-8. In this embodiment too, polymer in the core as well as at least some of the materials described for the container housing (*e.g.*, silicone and medical grade plastic) are non-metal biocompatible components that are in contact with the radiopaque marker. Langer Decl., ¶ 82.

i) "wherein said brachytherapy seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge)"

Crittenden teaches this limitation. Langer Decl., ¶ 83. Crittenden teaches seeds that are designed to be implanted through a "needle-like" "delivery chamber" that "can be about 0.010 to 0.050 inches in diameter." Crittenden at 8:50-61, 10:61-66 ("[T]he physician … can pre-load the delivery chamber with a plurality of pellets, each of which can be a minisphere, a helical, conical pellet, a cylindrical container, or other device capable of being implanted into the myocardium."). These diameters correspond to a range of between approximately 0.25 mm to 1.27 mm, meaning that any diameter in that range is less than about 2.7 mm. Crittenden also teaches in one embodiment that the seeds "can be formed as mini-spheres that are on the order of about 0.005 inches to about 0.040 inches in diameter." Crittenden at 9:46-48. These diameters too are suitable for passing through a needle having an interior diameter of less than about 2.7 mm. Langer Decl., ¶ 83.

j) "providing a brachytherapy implantation instrument comprising"

Crittenden teaches this limitation. Langer Decl., ¶ 84. Crittenden teaches an "apparatus for delivering therapeutic agents" that includes a "delivery chamber" with a "needle-like profile that is suitable for penetrating tissue." Crittenden at 3:44-53, 8:54-58. "The delivery chamber 14 is sized to hold the plurality of

minispheres 22, each of which contains a therapeutic agent." *Id.* at 7:53-55. "Upon positioning the delivery chamber adjacent the interior tissue wall of the heart, the physician drives the delivery chamber into the tissue and to the targeted area. The physician actuates the control mechanism and ejects a pellet from the delivery chamber, implanting the pellet within the targeted area of the myocardium." *Id.* at 11:39-46. This apparatus is pictured below in Figure 1.

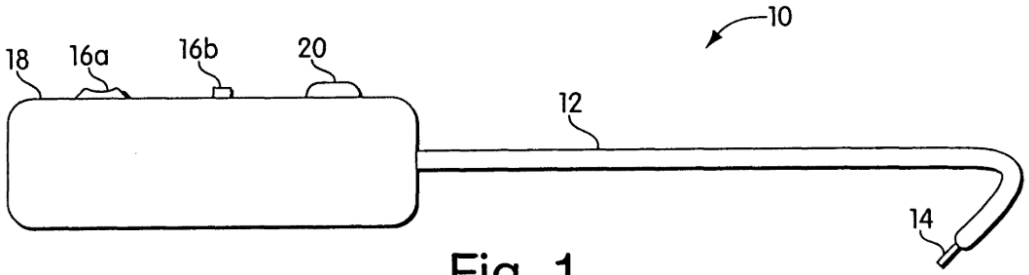


Fig. 1

Another embodiment of this device, one with a pistol grip, is disclosed in Figure 7 of Crittenden.

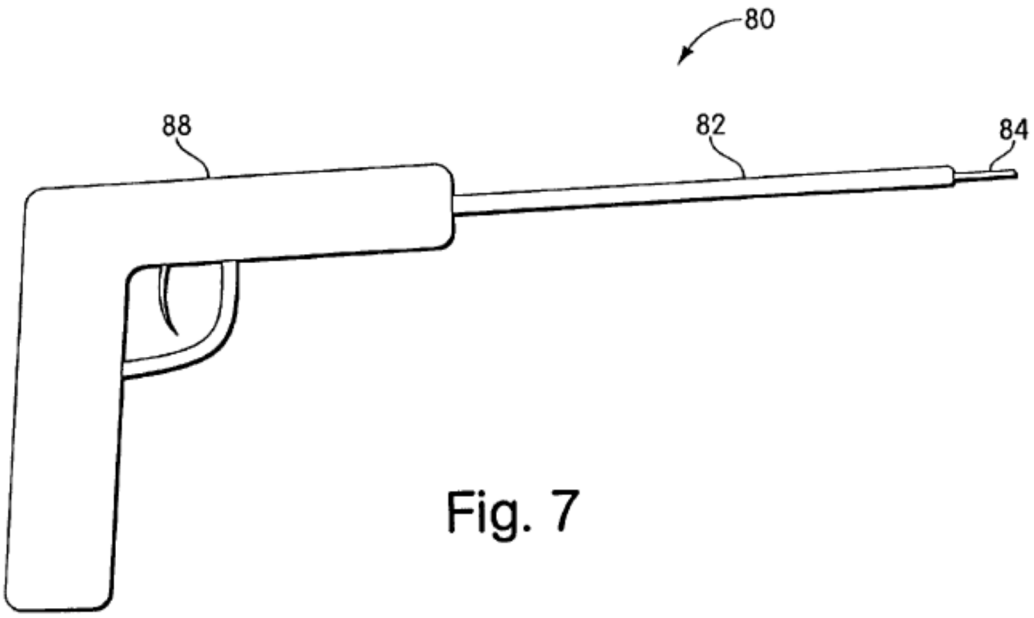


Fig. 7

Because Crittenden discloses a device that implants brachytherapy seeds (within the BRI of the ’193 Patent claims) Crittenden discloses this limitation.

k) “at least one brachytherapy implantation needle”

Crittenden teaches this limitation. Langer Decl., ¶ 85. Crittenden teaches an “apparatus for delivering therapeutic agents” that includes a “delivery chamber” with a “needle-like profile that is suitable for penetrating tissue.” Crittenden at 3:44-53, 8:54-58; *see also* 12:13-15 (“The delivery chamber 84 can be … dimensionally adapted to penetrate and extend through the pericardial sac.”). Crittenden further teaches that “the delivery chamber can be simply a hypodermic needle … .” *Id.* at 9:37; *see also id.* at 12:40-41. Crittenden therefore discloses a device having at least one brachytherapy implantation needle.

l) "having a bore having an interior diameter of less than about 2.7 millimeters (10 gauge)"

Crittenden teaches this limitation. Langer Decl., ¶ 86. Crittenden teaches that its seeds are designed to be implanted through a "needle-like" "delivery chamber" that "can be about 0.010 to 0.050 inches in diameter." Crittenden at 8:50-61, 10:61-66 ("[T]he physician … can pre-load the delivery chamber with a plurality of pellets, each of which can be a minisphere, a helical, conical pellet, a cylindrical container, or other device capable of being implanted into the myocardium."). These diameters correspond to a range of between approximately 0.25 mm to 1.27 mm, meaning that the bore of any interior diameter in this range will be less than about 2.7 mm. Langer Decl., ¶ 86.

m) "being adapted to accept the brachytherapy seed into the bore of the at least one brachytherapy implantation needle and deliver the accepted implantation device into a target tissue"[9]

Crittenden teaches this limitation. Langer Decl., ¶ 87. Crittenden teaches that the delivery chamber "is sized to hold the plurality of [seeds]." Crittenden at 7:53-55; *see also id.* at 10:61-66 ("[T]he physician … can pre-load the delivery chamber with a plurality of pellets, each of which can be a minisphere, a helical,

[9] For this IPR, Petitioner assumes the claimed "the accepted implantation device" is referring to the "brachytherapy seed."

conical pellet, a cylindrical container, or other device capable of being implanted into the myocardium."); Fig. 2A (depicting a delivery chamber holding seeds). "Upon positioning the delivery chamber adjacent the interior tissue wall of the heart, the physician drives the delivery chamber into the tissue and to the targeted area. The physician actuates the control mechanism and ejects a pellet from the delivery chamber, implanting the pellet within the targeted area of the myocardium." *Id.* at 11:39-46; *see also id.* at 12:15-17 ("The delivery chamber can penetrate into the myocardium and thereby allow the physician to implant pellets into the myocardium.").

n) "introducing the brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument"

Crittenden teaches this limitation. Langer Decl., ¶ 88. Crittenden teaches that "the physician … can pre-load the delivery chamber with a plurality of pellets, each of which can be a minisphere, a helical, conical pellet, a cylindrical container, or other device capable of being implanted into the myocardium." Crittenden at 10:61-66; Fig. 2A (depicting a delivery chamber holding seeds. "Alternatively, pellets containing a desired therapeutic agent can be preloaded into the delivery system, which is provided to the physician as a sterile, disposable item." *Id.* at 11: 3-5.

o) "introducing at least a portion of the at least one brachytherapy implantation needle into a target tissue in the subject"

Crittenden teaches this limitation. Langer Decl., ¶ 89. Crittenden teaches that "[u]pon positioning the delivery chamber adjacent the interior tissue wall of the heart, the physician drives the delivery chamber into the tissue and to the targeted area." Crittenden at 11:39-46; *see also id.* at 9:8-10 ("The delivery chamber 50 implants drug pellets having a hollow, conical shape which facilitates the penetration of the implants 60 into the tissue wall.").

p) "actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue"

Crittenden teaches this limitation. Langer Decl., ¶ 90. Crittenden teaches that "[t]he physician actuates the control mechanism and ejects a pellet from the delivery chamber, implanting the pellet within the targeted area of the myocardium." Crittenden at 11:42-46; *see also* 4:20-24, 12:28-30.

2. Claim 2

a) "The method of claim 1, wherein the target tissue is a diseased tissue"

Crittenden teaches the seed of claim 1 as previously discussed in Section VII.A.1. Crittenden also teaches this limitation. Langer Decl., ¶ 91. Crittenden teaches that it is "an object of the invention to provide methods of treatment of a coronary artery or cardiac indication that provide a longer duration of drug

pendency at the site of a localized disease." Crittenden at 3:8-11; *see also id.* at 1:18-47, 3:19-44 ("[T]he invention provides systems and methods for delivering a therapeutic agent into the myocardial tissue wall for treating various vascular conditions including restenosis, ischemic tissue, and myocardial infarction."). Crittenden further teaches that its "systems and methods for implanting depots of therapeutic agents can be applied to conditions other than those related to cardiac failure." *Id.* at 12:45-47. Accordingly, Crittenden teaches that the target tissue of its brachytherapy seeds is a diseased tissue. Langer Decl., ¶ 92.

B. Ground 2: Claims 1-2 Are Invalid as Obvious Over Crittenden in View of the '008 Patent

As explained above, Crittenden discloses every limitation of claims 1 and 2. For the same reasons, Crittenden renders those claims obvious whether considered alone or further in view of the disclosure of the '008 Patent. A POSA would be motivated to combine Crittenden and the '008 Patent and have a reasonable expectation of success because Crittenden expressly teaches that its systems can be used with the implants taught in the '008 Patent, incorporates the teachings in the '008 Patent by reference, and further teaches that a "radio-opaque metal core" can be incorporated into a "'container' type" implant, like those taught in the '008 Patent, "to facilitate viewing." Crittenden at 10:6-8; 10:24-30; Langer Decl., ¶¶ 68-69.

C. Ground 3: Claims 1-2 Are Invalid as Obvious Over Zamora in

View of Grimm

Zamora teaches all the limitations of claims 1-2 except for the express disclosure of a "brachytherapy implantation instrument," but which the '193 Patent itself acknowledges was conventional and known in the prior art. *E.g.* '193 Patent at 6:12-13; *see also* 6:20-21, 6:30, 11:23-28. To the extent Zamora does not alone obviate those claims, those claims are obvious in light of Zamora in combination with Grimm. Grimm teaches a prior art "brachytherapy implantation instrument" and "brachytherapy implantation needle" as described by the '193 Patent specification and thus further demonstrates that the claims are obvious in light of Zamora. Langer Decl., ¶¶ 93-127.

1. Motivation to Combine Zamora and Grimm

Zamora teaches that its brachytherapy implants are "implanted in a patient in a conventional manner, using methods substantially similar to those employed for treatment utilizing metal brachytherapy sources." Zamora at 13:46-49. Grimm teaches such a conventional method and device for implanting brachytherapy seeds. Grimm at 1:7-10, 1:46-52; Langer Decl., ¶¶ 94.

The '193 Patent acknowledges that brachytherapy implantation instruments and needles, like those taught in Grimm, were known in the prior art. *E.g.* '193 Patent at 6:12-13; 6:20-21, 6:30, 11:23-28. For example, the '193 Patent describes a "typical protocol for treating prostate cancer," in which "a specialized needle is

inserted through the skin between the rectum and scrotum into the prostate to deliver radioactive seeds to the prostate." '193 Patent at 1:38-45. This is the same method disclosed by Grimm. Grimm at Abstract, Fig. 1. Zamora too refers to the use of "seeds," like those it teaches, in "prostate brachytherapy." Zamora at 1:52-54. A POSA would therefore naturally have been led to the Grimm method of implanting brachytherapy seeds for implanting the brachytherapy seeds disclosed in Zamora. Langer Decl., ¶ 95. Because the implants in Zamora are intended to be used with the type of device disclosed in Grimm, a POSA would be both motivated to combine the teachings of Zamora and Grimm and would have had a reasonable expectation that Zamora's seeds could be implanted using the device and method of Grimm. *Id.*

2. Claim 1

a) "A method for administering a therapeutically active component to a target tissue in a subject, the method comprising the steps of"

Zamora teaches this limitation. Langer Decl., ¶ 96. Zamora teaches "methods and devices for the delivery of localized radioactivity, and preferably also concurrent delivery of localized chemotherapeutic, bioactive or other drugs to patients for therapeutic purposes," including chemotherapeutic agents, a radiosensitizer, an anti-angiogenesis compound, and natural or synthetic peptide hormones. Zamora at 5:19-22; *see id.* at 3:31-34, 3:57-61, 4:46-58, 5:19-27,

12:50-61, 13:1-16; cls. 9-11, 13-14, 16-17, 25-27; *see also* '083 PA at 4:20-23, 11:9-14. The method involves "placing the polymeric housing … in the affected tissue region of the patient." Zamora at 4:66-5:1; *see also* '083 PA at 13:14-14:8. Because these therapeutic agents, both radioactive and pharmaceutical, are delivered locally, the "target tissue" is the "affected tissue" in which the devices are implanted.

b) "providing a brachytherapy seed comprising"

Zamora teaches this limitation. Langer Decl., ¶ 97. Zamora discloses seeds, including those "shaped into a cylinder (or rod)" shape with the same general dimensions (*e.g.*, a "diameter of … 1.5 mm[] and a length [of] 6 mm") as those recited in the '193 Patent at 6:12-20. Zamora at Abstract, 4:11-14, 9:9-30, Fig. 7; *see also* '083 PA at 6:15-18, 7:11-25, Fig. 2. Zamora states that these seeds constitute a "brachytherapy device" for "treatment of an affected tissue region" such as a tumor. Zamora at 4:3-5, 1:46-55, 9:26-29; *see also id.* at Abstract, Figs. 1-7, 4:11-14, 4:22-25, 4:49, 4:51, 4:63-65, 5:8-10, 7:56-60, 8:1, 8:20-31, 9:9-24, 9:62-66, 10:49-52, cls. 1-17; *see also* '083 PA at 4:35, 6:15-18, 13:14-14:8.

c) "a non-metal biocompatible component"

Zamora teaches this limitation. Langer Decl., ¶ 98. Zamora teaches a non-metal biocompatible component comprising a polymeric implant housing, "made from a biocompatible and bioabsorbable polymeric material." Zamora at Abstract,

6:6-10, cls. 1-27; *see also* '083 PA at 6:20-7:10, 25-27. Zamora teaches that the "polymeric housing may be made from a biocompatible polymeric material." Zamora at 4:36-45 (listing exemplary non-metal polymers); *see also* '083 PA at 13:5-6.

Zamora further teaches that the device is filled with a "complex," including a polymer, that is "biocompatible, and preferably bioabsorabable," "non-toxic," and contains "bioabsorbable material." Zamora at 6:6-10, 10:17-18, 11:16-12:19; *see also* '083 PA at 6:30-31, 28. The complex may include a variety of non-metal biocompatible components, including fatty acids and polyethylene glycol. Zamora at 10:18-46; *see also* '083 PA at 9:20-25. Both the materials in the housing and complex comprise non-metal biocompatible components. Langer Decl., ¶ 99.

d) "a therapeutically active component comprising a non-radioactive drug"

Zamora teaches this limitation. Langer Decl., ¶ 100. Zamora teaches therapeutically active agents, including "chemotherapeutic, bioactive, or other drugs to patients for therapeutic purposes," including chemotherapeutic agents, a radiosensitizer, an anti-angiogenesis compound, and hormones. Zamora at 5:19-22; *id.* at 3:31-34, 3:57-61, 4:46-58, 5:19-27, 13:1-16, cls. 9-11, 13-14, 16-17, 25-27; *see also* '083 PA at 4:20-24, 11:9-14, 20. Specifically, Zamora teaches that the implant "may include a chemotherapeutic agent, including but not limited to" a long list of specific drugs—none of which are radioactive. Zamora at 12:50-61.

Zamora therefore teaches the inclusion of a therapeutically active component comprising a non-radioactive drug. *Id.*, ¶¶ 100-101.

e) "a radiopaque marker"

Zamora teaches this limitation. Langer Decl., ¶ 102. Zamora teaches that an issue facing those using its seeds is "verify[ing] the exact location of the devices of [the] invention within … the patient" because the devices' "polymeric material … is relatively transparent to X-rays, and the quantity of metal employed as the radioisotope, such as palladium or iodine, is not sufficient to permit easy visualization" of the implant. Zamora at 12:20-29. Zamora teaches that this issue "may be overcome by the use of a radiopaque medium." *Id.* at 12:28-29; *see also* '083 PA at 8:13-17. Zamora thus teaches that its devices "may further include a radiopaque medium," which Zamora defines as "a biocompatible radiopaque material capable of being detected by X-rays and conventional radiographic methods," including specific radiopaque mediums such as barium sulfate. *Id.* at 7:23-55; *see also id.* at Abstract, 4:19-24, 12:20-49, cls. 1, 12, 15, 18; *see also* '083 PA at 8:13-17. A POSA would recognize these materials, along with the others listed in Zamora, as radiopaque markers. Langer Decl., ¶ 102.

f) "said biocompatible component being"

As explained above at Section VII.C.2.c), Zamora discloses a biocompatible component.

g) "(a) physically associated with a therapeutically active component "

Zamora teaches this limitation. Langer Decl., ¶ 104. As discussed above at Section VII.C.2.c), Zamora's tube ("housing") comprises a biocompatible component. *Id.* In Zamora, the "drug" (a therapeutically active component) "may be disposed within at least a portion of the structure of the bioabsorbable polymeric housing," (i.e., biocompatible component), "such as a tube." Zamora at 4:19-24; 4:46-51; *see also* '083 PA at 11:9-14, 17. Additionally, Zamora teaches that the implant "may also include one or more coating constituents admixed with the therapeutic drug." Zamora at 4:54-55; *see also* '083 PA at 11:9-14, 17. Specifically, Zamora teaches that coating may include various "chemotherapeutic agent[s]," "radiosensitizer drug[s]," anti-angiogenesis compound[s]," or "hormones." Zamora at 12:50-61 (listing therapeutic agents). These drug-containing coatings are "applied to the tube." *Id.* at 13:17-19. Furthermore, the "tube 112 is … filled with a complex 126 that includes the radioisotope." *Id.* at 7:63-64. Therefore, the housing is a biocompatible component that is physically associated with a therapeutically active component. Langer Decl., ¶¶ 104-105.

h) "(b) in contact with said radiopaque marker"

Zamora teaches this limitation. Langer Decl., ¶ 106. As discussed above at Section VII.C.2.c), Zamora discloses that both its device's polymeric housing and interior complex 126 contains biocompatible components. Zamora teaches that the

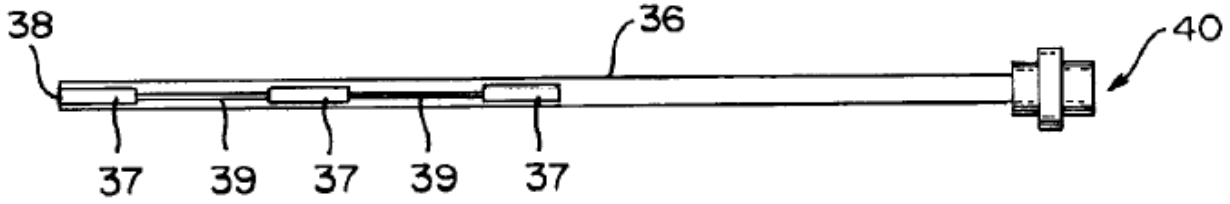
radiopaque marker "may be disposed within at least a portion of the structure of the bioabsorbable polymeric housing." Zamora at 4:19-24; *see also* '083 PA at 8:13-17. Zamora additionally teaches that the "barium-based radiopaque agent" may be "admixed" with the other elements in "complex 126" in the hollow interior of the housing. Zamora at 12:33-35, Fig. 7; *see also* '083 PA at 8:13-17. The radiopaque marker is therefore within the housing or is admixed in the inner complex, both of which are biocompatible components that are "in contact with" the radiopaque marker.

i) "wherein said brachytherapy seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge)"

Zamora and Grimm teach this limitation. Langer Decl., ¶ 107. Zamora teaches brachytherapy seeds that "may be made such that the exterior size is the same as … any other known … brachytherapy device." Zamora at 9:25-29; *see also* '083 PA at 6:15-18 ("seeds which approximate the size and shape of current art metal seeds"). Zamora specifically discloses a seed having a diameter of less than 2.7 mm. Zamora at 9:9-31; 9:62-10:1; *see also* '083 PA at 6:15-18, 7:11-25, Fig. 2. In one embodiment the "external diameter of tube 112 is 1.5 mm" and in another embodiment "the external diameter of tube 112 is 1.1 mm." Zamora at 9:9-10, 9:62-66; *see also* '083 PA at 7:11-25, Fig. 2. Such cylindrical seeds are of suitable shape and diameter for passing through the bore of a needle having a

diameter of less than about 2.7 mm, as shown below (37).

FIG. 2C



Grimm at Fig. 2C; Langer Decl., ¶ 107.

Moreover, the '193 Patent admits that prior art brachytherapy seeds like those taught in Zamora are sized to fit through an 18 gauge needle, which is smaller than a 10 gauge needle. '193 Patent at 2:5-8; *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. Thus, even without the teachings of Zamora and Grimm, this limitation would be obvious. Langer Decl., ¶ 108.

j) "providing a brachytherapy implantation instrument comprising"

Grimm discloses an instrument for "brachytherapy." Grimm at 1:46-50. Specifically, Grimm discloses "a needle combination, for use in radioactive seed implant treatment of prostate cancer" and an "accompanying method" of use. *Id.* at 2:38-40; Langer Decl., ¶109.

The '193 Patent concedes that "conventional brachytherapy seed implantation devices," like those taught in Grimm, were known in the prior art. *E.g.* '193 Patent at 6:12-13, 6:20-21, 6:30, 11:23-28; *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34. Thus, even without the teaching in Grimm, this

limitation would be obvious. Langer Decl., ¶ 110.

k) "at least one brachytherapy implantation needle"

Grimm teaches this limitation. Langer Decl., ¶ 111. Grimm discloses an instrument with a "needle combination" in which "[n]eedle 36 is loaded … with successive radioactive seeds" prior to insertion through a previously inserted hollow sleeve 28. Grimm at 4:14-25. "The needle portion 36 of the needle combination is shown in FIG. 2.*c*." *Id.* at 4:14-15, Fig. 2C. Grimm therefore discloses a device having at least one brachytherapy implantation needle.

The '193 Patent admits that brachytherapy implantation instruments with needles were known in the prior art. '193 Patent at 6:20-22 ("[M]any conventional brachytherapy seed applicators make use of brachytherapy implantation needles."); *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. Thus, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 112.

l) "having a bore having an interior diameter of less than about 2.7 millimeters (10 gauge)"

Grimm teaches this limitation. Langer Decl., ¶ 113. Grimm discloses a brachytherapy implantation needle that "is approximately the same diameter as the insertion stylet 22," which "is a solid, small diameter (typically 19 gauge) surgical stainless steel insertion stylet 22." Grimm at 4:23-25, 3:54-57. A 19 gauge needle has a bore diameter smaller than that of a 10 gauge needle, and therefore has a bore

having interior diameter of less than 2.7 mm. Langer Decl., ¶ 113.

Furthermore, the '193 Patent admits that brachytherapy implantation needles having an interior diameter of less than about 2.7 millimeters were known in the prior art. '193 Patent at 6:20-22 ("[M]any conventional brachytherapy seed applicators make use of brachytherapy implantation needles about 17 to 18 gauge in size."); *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. Thus, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 114.

m) "being adapted to accept the brachytherapy seed into the bore of the at least one brachytherapy implantation needle and deliver the accepted implantation device into a target tissue"

Grimm teaches this limitation. Langer Decl., ¶ 115. Grimm discloses that the brachytherapy needle is "preloaded" with brachytherapy seeds and is therefore adapted to accept such seeds into its bore. Grimm at 3:24-26, 4:15-16; Langer Decl., ¶ 115. Grimm also teaches that the brachytherapy needle implants the devices in the target tissue upon withdrawal and is therefore adapted to deliver the accepted implantation device into a target tissue. Grimm at 4:41-45, Fig. 3E.

Zamora teaches that its brachytherapy seeds "may be of any shape or configuration" that "approximates the size and shape of current art metal devices." Zamora at 4:9-10, 5:63; *see also* '083 PA at 6:15-18. A POSA would understand that Zamora's seeds could be made to fit into the bore of the brachytherapy

implantation needle. Langer Decl., ¶ 116.

Furthermore, the '193 Patent admits that such brachytherapy implantation needles were known in the prior art. *E.g.* '193 Patent at 6:20-22 ("many conventional brachytherapy seed applicators make use of brachytherapy implantation needles"); *id.* at 2:5-6 (prior art brachytherapy seeds are "sized to fit down the bore of one of the needles used in the implantation device"); *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. For the same reason, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 117.

n) "introducing the brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument"

Grimm teaches this limitation. Langer Decl., ¶ 118. Grimm discloses that the brachytherapy needle 36 "is loaded … with successive radioactive seeds," or brachytherapy seeds 37. Grimm at 4:15-16, 3:23-36, Fig. 2C. Grimm therefore discloses introducing the brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument.

Furthermore, the '193 Patent admits that the introduction of brachytherapy seeds into the bores of implantation needles was known in the prior art. '193 Patent at 1:46-2:2 (referring to a prior art brachytherapy "seed … forced down the bore of the needle"); *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-

34, 11:23-28. Thus, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 119.

o) "introducing at least a portion of the at least one brachytherapy implantation needle into a target tissue in the subject"

Grimm teaches this limitation. Langer Decl., ¶ 120. Grimm discloses that after "hollow sleeve 28 is inserted over the insertion stylet 22 into the prostate," and after "[i]nsertion stylet 22 is withdraw from sleeve 28, leaving just sleeve 28 in place," the brachytherapy needle 36 "is then inserted into sleeve 28" such that the end 38 of the needle is coincident with the tip of sleeve 28." Grimm at 4:3-4, 4:22-29.

At least a portion of the brachytherapy needle 36 is thereby introduced into the prostate 33, which is the target tissue in the subject. *Id.* at 1:7-10 ("This invention relates generally to radioactive seed implant treatment for prostate cancer and more specifically to a new needle combination for implanting such seeds into the prostate."), Fig. 3D; Langer Decl., ¶ 121.

Furthermore, the '193 Patent admits that the introduction of at least a portion of the brachytherapy implantation needle into the target tissue was known in the prior art. '193 Patent at 1:38-41 ("an implantation device having a specialized needle is inserted through the skin … to deliver radioactive seeds to the prostate"); *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. The

’193 Patent also identifies “[a] number of [prior art] devices [that] have been employed to implant radioactive seeds in tissues” that disclose this limitation. *Id.* at 1:34-38; U.S. Patent No. 6,007,474 at 1:66-2:5 (device implants brachytherapy seed “in body tissue in a channel that had resulted from the penetration of the barrel into the body tissue to be treated”). Thus, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 122.

p) “actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue”

Grimm teaches this limitation. Langer Decl., ¶ 123. Grimm discloses that after the brachytherapy needle 36 has been inserted into the prostate, “[i]mplant stylet 44 is also in place in the near end of the needle, abutting the nearest seed.” Grimm at 4:25-27. “[I]mplant stylet 44 is held in position by the operator while needle 36 and sleeve 28 together are slowly withdrawn, leaving a line of seeds … along the line vacated by the withdrawing needle/sleeve.” *Id.* at 4:41-45. The brachytherapy implantation instrument is thereby actuated such that the brachytherapy seed 37 is delivered through the bore of the brachytherapy implantation needle into the target tissue 33. *Id.*, Fig. 3E.

Furthermore, the ’193 Patent admits that actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue was known in

the prior art. '193 Patent at 1:46-49; *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. The '193 Patent also discloses "[a] number of [prior art] devices [that] have been employed to implant radioactive seeds in tissues" that disclose this limitation. *Id.* at 1:34-38; U.S. Patent No. 6,007,474 at 2:5-8 ("Upon each actuation of the spring-loaded trigger, the barrel retracts one seed length, depositing yet another seed in the tunnel created by the penetration of the barrel through the body tissue."). Thus, even without the teaching in Grimm, this limitation would be obvious. Langer Decl., ¶ 124.

3. Claim 2

a) "The method of claim 1, wherein the target tissue is a diseased tissue"

Zamora and Grimm teach the seed of claim 1 as previously discussed in section VII.C.2. Zamora and Grimm also teach this limitation. Langer Decl., ¶ 125. Zamora teaches that "it is an object of this invention to provide a … device for use in treatment of disease, including … cancers." Zamora at 5:57-60. Zamora teaches that its "brachytherapy" implants should "approximat[e] the density of the tissue in which the devices … are placed," which includes "cancerous tissues." *Id.* at Abstract; 13:24-38; *see also* '083 PA at 13:14-14:8. Therefore, Zamora teaches that the target tissue of its brachytherapy seeds is a diseased tissue.

Similarly, Grimm discloses an instrument and method for "radioactive seed implant treatment for prostate cancer" in which "such seeds [are implanted] into

the prostate." Grimm at 1:7-10. Therefore, Grimm also teaches that the target tissue for its instrument and method is a diseased tissue. Langer Decl., ¶ 126.

Furthermore, the '193 Patent admits that the target tissue being a diseased tissue was known in the prior art. '193 Patent at 1:23-27; *id.* at 1:27-28; *see also id.* at 1:23-28, 1:34-41, 1:46-69, 1:50, 2:5-10, 6:12-34, 11:23-28. Thus, even without the teaching in Grimm, this limitation would be obvious to one of skill in the art. Langer Decl., ¶ 127.

D. Ground 4: Claim 1 Is Invalid as Obvious Over De Nijs in View of Schopflin and Mascarenhas 1998

The De Nijs and Schopflin references teach implantable polymer devices that release a hormone to provide a contraceptive effect, and Mascarenhas 1998 teaches a device for implanting such devices. A POSA at the relevant time would have viewed De Nijs in combination with Schopflin and Mascarenhas 1998 as teaching each element of claim 1 of the '193 Patent. Langer Decl., ¶ 128.

Patent Owner argues that claim 1 is not limited to brachytherapy (*see* supra Section VI.A), if that is true then De Nijs teaches every limitation of the seed in claim 1 of the '193 Patent, except for "a radiopaque marker." Langer Decl., ¶ 129. Schopflin fills that gap, teaching a seed that includes "a radiopaque marker." *Id.*, ¶ 130.

In addition, De Nijs teaches "an implant of such small dimensions that it can be fitted subcutaneously with an ordinary hypodermic needle." De Nijs at 1:11-13;

1:67-2:2. Mascarenhas 1998 provides further details regarding the implantation instrument used to implant the specific seed described in De Nijs. Langer Decl., ¶ 129.

1. Motivation to Combine De Nijs, Schopflin, and Mascarenhas 1998

A POSA would have been motivated to combine De Nijs and Schopflin. *See* Langer Decl., ¶ 132. First, both De Nijs and Schopflin are in the same field and directed to the same applications, *i.e.*, polymer implants for the delivery of contraceptive hormones. *Id.* Moreover, both references describe implants with similar configurations, including ones with a polymeric coating surrounding a core enriched with the contraceptive hormone. *Id.* Additionally, both De Nijs and Schopflin teach polymer implants of a size and shape suitable to injection by hypodermic needle. *Id.* Thus, these references are from the same field of endeavor (biocompatible polymer implants for the controlled delivery of a drug). *Id.* A POSA would be motivated to combine them. *Id.*

Second, a POSA working with De Nijs's disclosure of a cylindrical hormone-eluting implant would have been motivated to incorporate Schopflin's teaching of including a radiopaque marker because it was known in the art to use radiopaque markers both to allow for precise placement of implants and to track their location within the body. *Id.*, ¶ 133, 137; Thiery 2000 (Ex. 1036) at 149; Botash 1997 (Ex. 1037) at 374; U.S. Pat. No. 5,788,980 (Ex. 1042) at 4:22-26.

This is particularly true for the non-biodegradable implants, like those disclosed in De Nijs, which must eventually be removed and were known in the art to be at risk of migrating within the patient, or to have been improperly inserted, and thus may be difficult to locate when the time comes to remove them. *Id.*, ¶¶ 134-138; *see, e.g.*, Thomsen 1985 at 224; Twickler 1992 (Ex. 1030) at 572-73; Thurmond 1994 (Ex. 1032) at 581 ("there is a need for an effective imaging method with which to localize capsules that are not easily palpable"); Lantz 1997 (Ex. 1034) at 323; Physician's Desk Reference (Ex. 1031) at 3346 (noting if Norplant capsules "cannot be palpated, they may be localized via ultrasound (7MHz), X ray, or compression mammography"); Sarma 1996 at 161 (Ex. 1033) ("Soft tissue plain x-ray … identified the implants clearly … [and] is less expensive than ultrasound examination."); Merki-Feld 2001 (Ex. 1035).

A POSA would also have had a reasonable expectation that the teachings of De Nijs and Schopflin could be successfully combined because they disclose implants with features that heavily overlap. Langer Decl., ¶ 139. De Nijs and Schopflin both teach cylindrical implants about 1.5 mm in diameter and 1 to 4 cm in length. *Compare* De Nijs at 1:62-67, 2:18-22 *with* Schopflin 9:4-22 (Example 3), 9:24-39 (Example 4) (describing cylindrical implants "of a length of 20 mm and a diameter of 1.5 mm"). Both teach the use of contraceptive hormones as the drug inside the implant. *Compare* De Nijs at 2:3-29 *with* Schopflin at 5:54-6:13.

Both teach the use of a polymeric coating to cover the implant. *Compare* De Nijs at 1:34-36, 2:3-20, 3:34-36 *with* Schopflin at 1:21-26, 7:2-4. Because Schopflin teaches that a radiopaque marker can successfully be incorporated into a similarly designed drug-releasing contraceptive implant, a POSA would have an expectation that radiopaque marker of Schopflin could be successfully combined with the De Nijs implant. Langer Decl., ¶ 139.

In a related proceeding, Patent Owner has asserted that Merck's arguments in the prosecution of its own patent (U.S. Patent No. 8,722,037) are relevant here. First, the prosecution history of an unrelated patent has no bearing on the obviousness of the '193 Patent and does not bind Merck. Also, the statements Patent Owner quotes (to the effect that a POSA would not be motivated to combine a radiopaque marker with De Nijs) are taken out of context. The Examiner in the '037 Patent prosecution repeatedly stated that adding a radiopaque marker to De Nijs was "prima facie obvious." *See e.g.*, '725 App., 4/22/10 Rejection (Ex. 1052) at 5. After multiple rejections, Merck was only able to overcome those rejections by repeatedly amending its claims to capture the unexpected results disclosed in the detailed experimental data of the '037 specification, requiring a particular "percent weight" for each component and that "substantially all the radio-opaque material is encapsulated in the thermoplastic polymer and not in the crystalline desogestrel or 3-ketodesogestrel." *See* '037 Patent cl. 1; '725 App., 12/18/12

Remarks (Ex. 1039) at 7-8. The '193 Patent contains no such guidance or data, and its claims have no such limitations.

A POSA would have been motivated to combine De Nijs and Schopflin with Mascarenhas 1998 because the implantation device disclosed in Mascarenhas 1998 is designed for use with subcutaneous contraceptive implants like those disclosed in De Nijs and Schopflin. Mascarenhas 1998 at S79; Langer Decl., ¶ 140. Both De Nijs and Mascarenhas 1998 are directed to the use of a rod-shaped EVA implant containing the same drug that is implanted subcutaneously using a needle to provide a contraceptive effect. Mascarenhas 1998 at S79; De Nijs at Abstract. The dimensions of the Implanon® implant for which the device of Mascarenhas 1998 is designed are in fact identical to those disclosed in De Nijs. *Compare* Mascarenhas 1998 at S79 *with* De Nijs at 7:47-60. Likewise, De Nijs contemplates that its implants "can be fitted subcutaneously with an ordinary hypodermic needle." De Nijs at 1:11-13. Because the implantation device disclosed in Mascarenhas 1998 was designed for use with contraceptive implants like those in De Nijs and Schopflin, a POSA would have a reasonable expectation that these references could be successfully combined. Langer Decl., ¶ 140.

2. Claim 1

a) "A method for administering a therapeutically active component to a target tissue in a subject, the method comprising the steps of"

De Nijs teaches this limitation. Langer Decl., ¶ 141. De Nijs teaches "an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally." De Nijs at 1:8-11; *see also id.* at Abstract, 1:20-23, 2:4-29, 3:46-57, cls. 1, 4.

b) "providing a brachytherapy seed comprising"

De Nijs teaches this limitation. Langer Decl., ¶ 142. De Nijs teaches an implant that is "virtually cylindrical with a maximum section of about 2 mm" and having a "length [that is] preferably between 1 and 4 cm." De Nijs at 1:62-67; *see also id.* at 3:19-24, 5:55-66, 6:35-53, 7:11-24, cl. 5. The '193 Patent teaches a brachytherapy seed in which "[a] drug or other therapeutically active substance can be included in the seed in addition to, or as an alternative to, a radioisotope." '193 Patent at 2:60-62. Because De Nijs teaches a seed that administers a therapeutically active agent, as explained above at Section VII.D.2.a), De Nijs teaches the provision of a brachytherapy seed.

c) "a non-metal biocompatible component"

De Nijs teaches this limitation. Langer Decl., ¶ 143. De Nijs teaches that "[i]n theory any polymeric material is suitable for the development of an implant provided only that it is biologically compatible." De Nijs at 1:34-36; *see also id.* at 2:41-61, cls. 1-3. De Nijs teaches that the implant coating and core may be comprised of "EVA," and even discloses specific brands of such, like Evatane®.

Id. at 2:3-62. These are all non-metal biocompatible components. Langer Decl., ¶ 143.

d) "a therapeutically active component comprising a non-radioactive drug"

De Nijs teaches this limitation. Langer Decl., ¶ 144 De Nijs teaches "an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally." De Nijs at 1:8-11; *see also id.* at Abstract, 1:20-23, 2:3-29, 3:46-57, cls. 1, 4. De Nijs teaches embodiments wherein the contraceptive agent is "3-keto-desogestrel, levonorgestrel, or gestodene active contraceptive substances." *Id.* at 2:3-13.

e) "a radiopaque marker"

Schopflin teaches this limitation. Langer Decl., ¶ 145. Schopflin teaches that a "radiopaque amount of barium sulfate" can be added to its seeds for the purpose of "improved X-ray localization in the body." Schopflin at 7:37-43. Schopflin Example 3 describes a cylindrical implant comprising a homogenous mixture of therapeutic agent, biocompatible polymer and barium sulfate. *Id.* at 9:5-21. Thus, Schopflin teaches an implant with a radiopaque marker (*i.e.*, barium sulfate).

f) "said biocompatible component being"

As explained above at Section VII.D.2.c), De Nijs discloses a biocompatible component.

g) "(a) physically associated with a therapeutically active component "

De Nijs teaches this limitation. Langer Decl., ¶ 147. De Nijs teaches seeds consisting of a core material containing EVA and a contraceptive hormone. De Nijs at Abstract, 1:20-23, 1:34-45, 1:62-67, 2:3-22; 2:66-3:2, 4:3-37. For instance, in example 1 the "active substance 3-keto-desogestrel and EVA core material" are "mixed," "processed into pellets by means of an extruder," and then transferred to a "co-axial extrusion apparatus" to produce a co-axial implant with the EVA and contraceptive hormone in the core. *Id.* at 3:63-4:10. Accordingly, at least the biocompatible component (EVA) in the core is physically associated with the contraceptive hormone. Langer Decl., ¶ 148.

h) "(b) in contact with said radiopaque marker"

De Nijs and Schopflin teach this limitation. Langer Decl., ¶ 148-49. Schopflin teaches seeds comprising a radiopaque marker (barium sulfate) mixed with a biocompatible component (organopolysiloxane). Schopflin at 9:5-22, 12:30-56.

As explained above at Section VII.D.2.b), De Nijs discloses a co-axial implant consisting of an EVA-drug. Thus, if one combines the teaching in of the radiopaque marker in Schopflin with the seed taught in De Nijs by adding that marker to either the core or skin, the radiopaque marker will be in contact with the biocompatible component and therapeutically active agent in the core. Langer

Decl., ¶ 149.

i) "wherein said brachytherapy seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge)"

De Nijs teaches this limitation. Langer Decl., ¶ 150. De Nijs teaches that "[t]he implant of the invention is cylindrical … with a maximum section of about 2 mm, but preferably between 1.5 and 2.0 mm." De Nijs at 1:62-64, 5:47-67 (teaching an embodiment with a 1.95 mm external diameter); *see* also *id.* at 2:3-29, 3:19-24, Ex. 5, cl. 5. De Nijs also teaches that the maximum diameter of the implant is 2 mm so as to be small enough to allow "subcutaneous fitting … with an ordinary hypodermic needle." *Id.* at 1:62-2:2. De Nijs therefore teaches that the brachytherapy seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 mm.

Mascarenhas 1998 further teaches this limitation, stating that the Implanon® rod has a diameter of 2 mm and that it comes "preloaded" in the disposable applicator used for insertion. Mascarenhas 1998 at S79; Langer Decl., ¶ 151.

j) "providing a brachytherapy implantation instrument comprising"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 152. Mascarenhas 1998 teaches a "disposable applicator preloaded with an Implanon rod … for insertion." Mascarenhas 1998 at S79. The device is designed to implant

the Implanon® rod, which is a "contraceptive implant," under the skin "of the nondominant upper-arm." *Id.* Therefore, applying the construction explained above in Section VI.A, Mascarenhas 1998 discloses a brachytherapy implantation instrument.

k) "at least one brachytherapy implantation needle"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 153. Mascarenhas 1998 teaches a device which comprises a "needle" which is "introduced directly under the skin" to implant the Implanon® device. Mascarenhas 1998 at S79-80, Fig. 1.

l) "having a bore having an interior diameter of less than about 2.7 millimeters (10 gauge)"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 154. Mascarenhas 1998 teaches that its brachytherapy implantation needle is "preloaded" with an Implanon® rod having a "diameter of 2 mm." Mascarenhas 1998 at S79. A POSA would understand that the bore of said needle therefore has a diameter of less than about 2.7 millimeters. Furthermore, De Nijs teaches that its implants "can be fitted subcutaneously with an ordinary hypodermic needle." De Nijs at 1:11-13. A POSA would understand that ordinary hypodermic needles have bore sizes of 10 gauge or smaller. Langer Decl., ¶ 154. Mascarenhas 1998 and De Nijs therefore teach a brachytherapy implantation needle having a bore having an interior diameter of less than about 2.7 mm.

m) "being adapted to accept the brachytherapy seed into the bore of the at least one brachytherapy implantation needle and deliver the accepted implantation device into a target tissue"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 155. Mascarenhas 1998 teaches that its brachytherapy implantation needle is "preloaded with an Implanon rod," which is a "brachytherapy seed" under proposed construction. Mascarenhas 1998 therefore teaches a brachytherapy implantation needle that is adapted to accept a brachytherapy seed into its bore. *Id.* Mascarenhas 1998 also teaches that the device is used to insert an Implanon® rod "into the inside of the nondominant upper-arm." Mascarenhas 1998 at S79. Mascarenhas 1998 therefore teaches a brachytherapy implantation needle adapted to deliver the accepted implantation device into a target tissue.

n) "introducing the brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 156. Mascarenhas 1998 teaches that its brachytherapy implantation needle is "preloaded with an Implanon rod," which is a "brachytherapy seed" under proposed construction. Mascarenhas 1998 at S79. Mascarenhas 1998 therefore teaches a introducing a brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument.

o) "introducing at least a portion of the at least one brachytherapy implantation needle into a target tissue in the subject"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 157.

Mascarenhas 1998 teaches that "[t]he needle is introduced directly under the skin" at the site of implantation. Mascarenhas 1998 at S79. Mascarenhas 1998 therefore teaches introducing at least a portion of the at least one brachytherapy implantation needle into a target tissue in the subject.

p) "actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue"

Mascarenhas 1998 teaches this limitation. Langer Decl., ¶ 158.

Mascarenhas 1998 teaches actuating the device in "the reverse of an injection." Mascarenhas 1998 at S79. To actuate the device, the "cannula is slowly pulled out of the arm while keeping the obturator tightly fixed in place." *Id.* The obturator there leaves the Implanon® implant in place under the skin, pushing it out of the bore of the needle as the device is withdrawn. Mascarenhas 1998 therefore teaches actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue.

VIII. THE ASSERTED GROUNDS ARE NOT CUMULATIVE

Four grounds are asserted in this petition. Ground 1 is not cumulative of

Grounds 2-4 because it is based on section 102, rather than section 103. Grounds 3-4 are not cumulative of each other because the De Nijs and Schopflin references are directed to contraceptive devices, rather than brachytherapy devices. As explained above, Patent Owner has taken the position that claim 1 encompasses contraceptive devices, notwithstanding the express claim language.

Further, Crittenden and Schopflin were not cited during prosecution of the '193 Patent or any related application and Zamora, Grimm, and De Nijs were not cited during prosecution of the '193 Patent. Accordingly, *none* of the references in the proposed grounds was previously considered during prosecution of the '193 Patent.

IX. MANDATORY NOTICES

A. Related Matters, Real Party-in-Interest, Filing Fee, Lead and Backup Counsel

Related Matters: On June 5, 2017, the Patent Owner filed a patent infringement suit against Merck & Co., Inc., Merck Sharp & Dohme Corp., N.V. Organon, and Merck Sharp & Dohme B.V. in the U.S. District Court for the District of New Jersey: *Microspherix LLC v. Merck Sharp & Dohme Corp.*, No. 2:17-cv-03984-CCC-JBC (D.N.J.). The Patent Owner has since filed an amended complaint, dismissing N.V. Organon and Merck & Co., Inc. and adding Organon USA, Inc., as a defendant. Defendants in these actions are accused of infringing the '193 Patent and three related patents, U.S. Patent Nos. 9,636,402, 9,636,401,

and 8,821,835 ("the '835 Patent"). Petitions for IPR of the '402, '401, and '835 Patents were recently filed in IPR2018-00393, IPR2018-00402, and IPR2018-00602.

Real Parties in Interest: Merck Sharp & Dohme Corp., Merck Sharp & Dohme B.V., and Organon USA, Inc. are the real parties-in-interest.

Fees and Credits: The Patent Trial and Appeal Board is hereby authorized to charge any fees or credit any overpayment to Deposit Account 501408.

Designation of Counsel: Petitioners designate the following Lead and Back-up Counsel. Concurrently filed with this Petition are Powers of Attorney per 37 C.F.R. § 42.10(b). Service via hand-delivery may be made at the postal mailing address designated below. Petitioners consent to electronic service by e-mail.

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X. RELIEF REQUESTED

Petitioners request *inter partes* review of the '193 Patent, and cancellation of

claims 1-2 of the ’193 Patent under 35 U.S.C. §§ 102 and 103.

DATED: June 18, 2018

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CERTIFICATE OF WORD COUNT

The undersigned certifies that, pursuant to 37 C.F.R. § 42.24(d), the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,514,193 contains, as measured by the word processing system used to prepare this paper, 13,998 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

DATED: June 18, 2018

By: /Tracey Davies/

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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), (b) on the Patent Owner via Federal Express of a copy of this Petition for *Inter Partes* Review and supporting materials at the correspondence address of record for the '193 Patent:

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