IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

INTEGRA LIFESCIENCES CORP., INTEGRA LIFESCIENCES SALES LLC, CONFLUENT SURGICAL, INC., and INCEPT LLC,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 15-819-LPS-CJB
HYPERBRANCH MEDICAL TECHNOLOGY, INC.,	)	
Defendant.	)	

REPORT AND RECOMMENDATION

1. In this action filed by Plaintiffs Integra LifeSciences Corp., Integra LifeSciences Sales LLC, Confluent Surgical, Inc. and Incept LLC (collectively, "Plaintiffs" or "Integra") against Defendant HyperBranch Medical Technology, Inc. ("HyperBranch" or "Defendant"), Plaintiffs allege infringement of a number of patents (collectively, the "patents-in-suit" or "asserted patents"), including United States Patent Nos. 8,535,705 (the "'5705 patent") and 7,009,034 (the "'034 patent"). Presently before the Court is the issue of claim construction regarding what the Court will refer to herein as the "biocompatible" claim terms. These terms are found in the preambles of the asserted claims of the '5705 patent and the '034 patent. (D.I. 520, 525, 544, 546)

2. The Court incorporates by reference herein the discussion of general principles of claim construction set out in its July 27, 2017 Report and Recommendation. (D.I. 307 at 5-7)

3. The Court has recently determined that the preambles from asserted claims 1, 6,

12 and 17 of the '5705 patent[1] and asserted claim 10 of the '034 patent[2] are limiting. (D.I. 483, 543) These preamble phrases require a "biocompatible . . . hydrogel" or a "[biocompatible] composition[,]" respectively. (D.I. 520 at 1; D.I. 525 at 3-4; *see also* D.I. 483 at 8) The present dispute is the proper claim construction for the "biocompatible hydrogel/composition"

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[1] Claim 1 of the '5705 patent, from which claims 6, 12 and 17 depend, recites:

> **1.** A method of making a *biocompatible degradable hydrogel* to treat a medical condition of a patient comprising:
> identifying a medical condition for treatment by use of a hydrogel formed in situ in a patient and fully degradable in a patient in less than about 180 days; and
> mixing a first precursor with a second precursor in situ in the patient to form the hydro gel for treatment of the medical condition,
> with the first biocompatible synthetic hydrophilic polymer precursor having a water solubility of at least 1 gram per 100 milliliters and comprising at least two electrophilic functional groups; and the second biocompatible synthetic hydrophilic polymer precursor comprising at least two nucleophilic amine functional groups . . . .

('5705 patent, col. 30:34-47 (emphasis added))

[2] Claim 1 of the '034 patent, from which asserted claim 10 depends, recites:

> **1.** A method of preparing a *composition suitable to coat a tissue of a patient*, the method comprising:
> mixing reactive precursor species comprising nucleophilic functional groups, reactive precursor species comprising electrophilic functional groups, and a visualization agent such that the nucleophilic functional groups and electrophilic functional groups crosslink after contact with the tissue to form a hydrogel having an interior and an exterior, with the exterior having at least one substrate coating surface and the visualization agent being at least partially disposed within the interior and reflecting or emitting light at a wavelength detectable to a human eye to thereby provide a means for visualization of the coating by a human eye.

('034 patent, cols. 39:56-40:2 (emphasis added)) Claim 10 adds that the hydrogel forms within 5 seconds after contact with the substrate. (*Id.*, col. 40:23-24)

limitations of these claims. (D.I. 520, 525, 544, 546) Plaintiffs propose that "biocompatible" be construed to mean "'not harmful to living tissue.'"[3] (D.I. 520 at 1) Defendant proposes that "biocompatible hydrogel/composition" be construed to mean "'a hydrogel/composition formed from crosslinked biocompatible precursors.'" (D.I. 525 at 4) For the following reasons, the Court recommends that Defendant's proposal be adopted.

4. The asserted patents themselves do not expressly define "biocompatible." In support of its proposal, then, Defendant starts elsewhere. It asserts that the term "biocompatible" is a broad one, with no universally accepted definition to a person of ordinary skill in the art ("POSITA"). (D.I. 525 at 4 (citing D.I. 528 at ¶ 15)); *see also Marine Polymer Techs., Inc. v. HemCon, Inc.*, 672 F.3d 1350, 1358 (Fed. Cir. 2012) (noting that "the district court did not find that 'biocompatible' had a plain and ordinary meaning to one skilled in the art"). Defendant's expert, Dr. Anthony Lowman, opined that "biocompatible" is a "term of degree that is inherently qualitative and open to subjectivity across a broad range of different accepted levels of 'biocompatibility.'" (D.I. 528 at ¶ 15) And indeed, the asserted patents support the notion that "biocompatible" is a term of degree, with the '034 patent's specification explaining that "[h]ydrogels are especially useful for use in the body because they are *more biocompatible* than non-hydrogels and are thus better tolerated in the body." ('034 patent, col. 1:52-54 (emphasis added)) Defendant also points out that dictionaries do not provide a universal definition for "biocompatible." One general-purpose dictionary defines "biocompatible," for example, to mean "compatible with living tissue, as a prosthetic material or device that is not rejected or does not

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[3] Plaintiffs further note that to the extent that the phrase "a biocompatible composition" is in need of construction, that term should be construed to mean "'a composition that is not harmful to living tissue.'" (D.I. 520 at 2-3)

cause infection[,]" (D.I. 528, ex. 27), while the *Williams Dictionary of Biomaterials* ("*Williams Dictionary*") provides a "preferred" definition for "biocompatibility" as "the ability of a material to perform with an appropriate host response in a specific application[,]" (*id.*, ex. 26 at 40). The *Williams Dictionary* explains that alternate definitions such as "the quality of not having toxic or injurious effects on biological systems" are "not recommended since [they] do not address the positive or desired component of interactions between biomaterials and host tissue." (*Id.*) All of these sources, then, suggest that the construction of "biocompatible" should not be unduly narrow.

5. From there, Dr. Lowman helps to move things forward by explaining that a POSITA understands that hydrogels are necessarily associated with being biocompatible "because they are water-swollen materials with properties that mimic human tissue[.]" (D.I. 527 at ¶ 23; *see also* D.I. 415, ex. 146 at ¶ 58 ("Hydrogels have been recognized as ideal candidates for biomedical applications because their water-swollen networks are highly biocompatible."))[4] Relatedly, the Court agrees with Defendant that: (1) the specifications of the asserted patents

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[4] The Ferland et al. reference regarding SprayGel that Plaintiffs point to as intrinsic evidence, (D.I. 544 at 4), explains that "SprayGel is a blue colored hydrogel film . . . . [b]ecause this hydrogel is composed mostly of water, it is highly biocompatible[,]" (D.I. 523, ex. 1 at ex. 10). And HyperBranch points out additional references, cited on the faces of certain of the patents-in-suit, (D.I. 546 at 3 n.1), that further indicate that a POSITA would understand that a hydrogel is necessarily "biocompatible." (*See* D.I. 548, ex. 192 (United States Patent No. 6,958,212 to Hubbell et al.), col. 25:11-15 ("Hydrogels are particularly useful for the delivery of protein therapeutics. Hydrogels are biocompatible, and provide a gentle environment for proteins[.]"); D.I. 413, ex. 134 (United States Patent No. 6,458,889 to Trollsas et al.), cols. 2:48-3:6 (explaining that a composition is provided "to give a biocompatible . . . matrix . . . . admixture of components A, B and C in an aqueous medium results in crosslinking of the composition to give a biocompatible . . . matrix"); D.I. 548, ex. 193 (United States Patent No. 6,174,645 to Russell et al.), col. 1:29-34 ("Hydrogels . . . because of their characteristic properties such as swellability in water, hydrophilicity, biocompatibility and lack of toxicity, have been utilized in a wide range of biological and medical applications."))

presume that when the recited crosslinked precursors are used to make a hydrogel, the result will be a "biocompatible hydrogel"; and (2) the patents make no mention of any *relative degree* of biocompatibility of the hydrogel. (D.I. 525 at 6; *see also* D.I. 546 at 2-3; D.I. 527 at ¶¶ 19, 24, 27; D.I. 528 at ¶ 16)

6. With respect to the '034 patent, for instance, under the heading "Preparation of Biocompatible Polymers[,]" the specification explains that "[s]everal biocompatible crosslinked hydrogels may be produced using the crosslinkers and functional polymers described in FIGS. **1** to **5**. Preferred combinations of such polymers suitable for producing such biocompatible crosslinked polymers are described in Table 2." ('034 patent, col. 22:40-44; *see also id.* at Abstract ("Biocompatible crosslinked polymers, and methods for their preparation and use, are disclosed in which the biocompatible crosslinked polymers are formed from water soluble precursors having electrophilic and nucleophilic functional groups capable of reacting and crosslinking in situ. Methods for making *the resulting biocompatible crosslinked polymers* biodegradable or not are provided . . . .") (emphasis added)) Further, the specification explains that Figure 8 "depicts the preparation of an electrophilic water soluble crosslinker or functional polymer . . . its crosslinking reaction with a nucleophilic water soluble functional polymer *to form a biocompatible crosslinked polymer product*[.]" (*Id.*, col. 4:27–31 (emphasis added))[5] And the specification of the '034 patent also indicates elsewhere that the reactive precursor species that are used to form the hydrogel are themselves biocompatible. (*See, e.g.*, *id.*, col. 2:18-19 ("The present inventors have realized that use of color in *biocompatible crosslinked polymers*

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[5] (*See also* '034 patent, col. 25:32-35 ("In some embodiments, it is preferred to apply the precursor solutions sequentially so as to 'prime' the tissue, resulting in improved adherence *of the biocompatible crosslinked polymer to the tissue.*") (emphasis added))

and precursors greatly improves their performance[.]"); *id.*, col. 4:49-51 ("FIG. **13** shows the variation in gelation time with the concentration of *biocompatible crosslinked polymer precursors*, and with the solution age of the 4 arm 10 kDa carboxymethyl-hydroxybutyrate-N-hydroxysuccinimidyl PEG [] electrophilic functional polymer" (emphasis added); *id.*, col. 4:60-62 ("The present inventors have realized that use of color *in biocompatible crosslinked polymers and/or reactive precursor species* improves the performance of crosslinked networks of polymers and/or reactive precursor species . . . .")).

7. Similarly, with respect to the '5705 patent, claim 1 itself recites a "method of making a biocompatible degradable hydrogel . . . comprising . . . mixing a first precursor with a second precursor . . . *with the first biocompatible* synthetic hydrophilic *polymer precursor* having a water solubility of at least 1 gram per 100 milliliters and comprising at least two electrophilic functional groups; *and the second biocompatible* synthetic hydrophilic *polymer precursor* comprising at least two nucleophilic amine functional groups . . . wherein mixing the first and the second synthetic hydrophilic polymer precursors forms crosslinking covalent bonds[.]" ('5705 patent, col. 30:34-61 (emphasis added)) Dr. Lowman thus opines that "the preamble's 'biocompatible . . . hydrogel' is the hydrogel that results from the crosslinking of the claimed biocompatible precursors." (D.I. 527 at ¶ 18) And like the specification of the '034 patent, the specification of the '5705 patent indicates that when the disclosed precursors are used, a biocompatible hydrogel necessarily will result. (*Id.* at ¶ 19; *see also, e.g.*, '5705 patent, Abstract ("Biocompatible crosslinked polymers, and methods for their preparation and use, are disclosed in which the biocompatible crosslinked polymers are formed from water soluble precursors having electrophilic and nucleophilic groups capable of reacting and crosslinking in situ."); *id.*,

col. 16:60-64 ("Several biocompatible crosslinked polymers may be produced using the crosslinkers and functional polymers described in FIGS. **1** to **5**. Preferred combinations of such polymers suitable for producing such biocompatible crosslinked polymers are described in Table 1 and Table 2.")) As HyperBranch points out, "[t]here is no . . . teaching that any of the hydrogels disclosed [in the asserted patents] are anything but 'biocompatible.'" (D.I. 546 at 2)

8. The Court now turns to why, in its view, Plaintiffs' proposal (that "biocompatible" in the context of these patents means "not harmful to living tissue") is not supported by the record. First, Plaintiffs assert that their proposal, which comes from the *Oxford Dictionary*, is the plain and ordinary meaning of the term. (D.I. 520 at 1 (citing D.I. 523, ex. 1 at ¶ 10); D.I. 466, ex. 7 (*Oxford Dictionary* defining "biocompatible" as "(especially of material used in surgical implants) not harmful or toxic to living tissue")) However, as described above, Defendant demonstrated (with support from Dr. Lowman and citations to various dictionary definitions) that the term "biocompatible" does *not* have any one universally accepted meaning to a POSITA.

9. Second, it is important to consider how Plaintiffs are interpreting their proposal. Plaintiffs assert that the POSITA would understand that: (1) whether a hydrogel is "not harmful to living tissue" is determined by "gross observation of foreign body response and histological evaluation of tissue for inflammation[;]" and (2) a hydrogel that, when used on tissue, results in tissue that appeared "normal with no inflammation or that showed histological mild inflammation" would be considered "biocompatible." (D.I. 520 at 3-6 (citing D.I. 523, ex. 1 at ¶¶ 8, 26)) Thus, in Plaintiffs' view, a hydrogel would *not* be biocompatible if, when used on tissue, it causes at least moderate inflammation of the tissue. (D.I. 544 at 5; *see also* D.I. 527 at ¶

35 (Dr. Lowman explaining that Dr. Mays is using "'not harmful to living tissue'" as a proxy for "the absence of any histological testing that indicates at least moderate inflammation of the tissue"); D.I. 525 at 9-10 (Defendant asserting if the Court does not adopt HyperBranch's construction, it should include the actual standard being applied by Plaintiffs and construe the full term as "'not harmful to a patient as demonstrated by the absence of any histological testing that indicates moderate or severe tissue inflammation'"))

10. With the asserted patents themselves not expressly defining "biocompatible" (or using the terms "harm" or "harmful" in connection with biocompatibility), where are Plaintiffs gleaning their interpretation of what "not harmful to living tissue" means in the context of these patents? Plaintiffs first point to United States Patent No. 6,312,725 ("Wallace"), which expressly defines the term "biocompatible" as "the ability of the compositions of the present invention to be applied to tissues without eliciting significant inflammation and fibrosis or other adverse tissue responses." (D.I. 423, ex. E (hereinafter, "Wallace"), col. 3:64-67)[6] Plaintiffs focus on

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[6] Plaintiffs assert that Wallace is intrinsic evidence to the '034 patent and the '5705 patents, since it is cited on the face of those patents. (D.I. 520 at 2 & n.3; D.I. 544 at 3) Indeed, the United States Court of Appeals for the Federal Circuit has explained that "prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence." *Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003); *see also V-Formation, Inc. v. Benetton Grp. SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005). Accordingly, at first blush, it seems appropriate to determine that "biocompatibility" in the asserted patents must carry the same meaning as the term "biocompatible" as used in Wallace.

However, as HyperBranch points out, the asserted patents are members of a patent family, and United States Patent No. 6,566,406 (the "'406 patent") is the parent application to the '034 patent and the '5705 patent. (D.I. 546 at 3) The '406 patent recites methods for preparing "a biocompatible crosslinked polymer hydrogel[,]" (*see* D.I. 1, ex. D, col. 30:29-30), and it does not cite to Wallace, nor was Wallace cited during prosecution of the '406 patent, (*see* D.I. 546 at 3). Generally, identical claims terms in related patents are construed consistently, and thus, because it does not appear that the patentee relied on Wallace to give meaning to "biocompatible" in the '406 patent, one would not expect that Wallace would inform the meaning

two tables in Wallace, Table 3 and Table 4 (depicted below), which relate to Example 4 (entitled "Enhanced Biocompatibility of Thioester-linked Formulations"). (Wallace, cols. 12:55-13:35)

TABLE 3

Grading Key for Biocompatibility Experiments

Score	Gross Observations	Histological Observations
	all tissues appeared normal	all tissues appeared normal, no inflammation
+	mild foreign body response	mild inflammation
++	moderate foreign body response	moderate inflammation
+++	marked foreign body response	marked inflammation
++++	severe foreign body response	severe inflammation

TABLE 4

Results for Biocompatibility Experiments

		Results	
Test	Description	Gross Observations	Histological Observations
A	surgical control	–	+
B	fibrillar collagen	–	+
C	20% w/v tetra-SG PEG 10,000 + 20% w/v tetra-amino PEG 10,000	++++	++++
D	20% w/v tetra-SG PEG 10,000 + 20% w/v tetra-sulfhydryl PEG 10,000	++	++
E	20% w/v tetra-SG PEG 10,000 + 20% w/v tetra-amino PEG 10,000; gelled ex-vivo; treated with mono-SG PEG 5000	+	++
F	20% w/v tetra-SG PEG 10,000 + 20% w/v di-sulfhydryl PEG 3,400; gelled ex-vivo; treated with di-amino PEG 3400	++++	++++

The specification then explains that "Experiment C shows a severe response to hydrogels made with amino-PEG. . . . By substitution of sulfhydryl-PEG for amino-PEG, as in Experiment D, the

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of the term in the '034 patent or the '5705 patent. (*Id.* (citing *Abtox, Inc. v. Exitron Corp.*, 131 F.3d 1009, 1010 (Fed. Cir. 1997)).

biocompatibility of the hydrogel is significantly improved. . . . Thus, these results show the enhanced biocompatibility of sulfhydryl formulations over amino formulations." (*Id.*, col. 13:38-58) Plaintiffs then assert that a POSITA would understand that moderate inflammation (of the type found in Experiment D) amounts to "significant inflammation"—especially in view of the "other intrinsic evidence" wherein "biocompatible" is used to refer to minimal or no inflammatory response or minimal or no adverse tissue reaction. (D.I. 544 at 5) Therefore, according to Plaintiffs, the POSITA would interpret the results of Experiment D (showing moderate foreign body response and moderate inflammation), to indicate that such hydrogel is *not* biocompatible. (*Id.*)[7]

11. When one turns to the "other intrinsic evidence" referred to above by Plaintiffs, one can see that the cited references are typically describing "biocompatibility" of a *high* degree. For example, United States Patent No. 5,514,379 explains that "[t]he hydrogel compositions described herein have *high biocompatibility*, e.g., they do not cause severe side effects, and low immunogenicity of both the primary materials and their degradation products, which allows repeated administration." (D.I. 523, ex. 1 at ex. 5, col. 3:45-50 (emphasis added)) United States Patent No. 5,410,016 states that "[t]he polymer shows *excellent biocompatibility*, as seen by a minimal fibrous overgrowth on implanted samples." (*Id.*, ex. 1 at ex. 6, col. 6:14-16 (emphasis added); *see also id.*, cols. 10:62-11:7 ("In a particularly preferred application . . . . [the method] is capable of creating uniform polymeric coating . . . which does not evoke thrombosis or localized

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[7] Dr. Lowman points out that Plaintiffs do not identify the relevant time period that was at issue in this testing disclosed by Wallace—i.e., how long after implantation was the testing? At what stage of the healing process? What was the overall healing response to the implanted hydrogels after degradation? (D.I. 527 at ¶ 37) According to Dr. Lowman, the testing in Wallace relates to a single study at an early point in time. (D.I. 528 at ¶¶ 10-11)

inflammation")) The Ferland et al. reference evaluating SprayGel states that, in a second look procedure performed after 3-16 weeks after treatment with SprayGel, "all treated surfaces look normal and appear to be healing normally[,]" and also notes that "[b]ecause this hydrogel is composed mostly of water, it is *highly biocompatible.*" (*Id.*, ex. 1 at ex. 10 (certain emphasis added, certain emphasis omitted)) In light of all of this, it is clear that to Plaintiffs, "not harmful to living tissue" means "highly biocompatible" (or causing no more than "mild" inflammation).

12. The Court is not convinced that Plaintiffs' reading here—that a "biocompatible" hydrogel is one that produces only "minimal or no inflammatory response or minimal or no adverse tissue reaction[,]" (D.I. 544 at 5)—is the correct one. As HyperBranch notes, Plaintiffs' proposal appears to be "inject[ing] an unsubstantiated *super*-biocompatibility requirement into the claims[.]" (D.I. 525 at 1 (emphasis in original))[8] This is inappropriate where the patents-in-suit do not refer to "highly biocompatible" hydrogels or hydrogels with "excellent" biocompatibility—they simply refer to "biocompatible" hydrogels. (D.I. 528 at ¶ 17 ("One of ordinary skill in the art recognizes that a definition of 'biocompatible' that merely reduces 'biocompatible' to harm, as Dr. Mays has done, is not a proper definition for the term."))

13. In sum, although the patents do not expressly define "biocompatible," they clearly

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[8] The Court also finds it notable that Wallace describes Experiment D, which showed moderate foreign body response and moderate inflammation (and which Plaintiffs are interpreting to mean not "biocompatible") as showing "biocompatibility [that has been] significantly improved" and having "enhanced" biocompatibility over formulations which showed severe foreign body response and severe inflammation. (Wallace, col. 13:41-58; *see* D.I. 527 at ¶ 37 (Dr. Lowman explaining that Wallace notes that for the CoSeal hydrogel described in Experiment D, "'the biocompatibility of the hydrogel is significantly improved' [and that Dr. Mays nevertheless] contends that even such a hydrogel with 'enhanced biocompatibility' does not satisfy his threshold for 'biocompatible' in the patents-in-suit"); *see also* D.I. 528 at ¶ 7) This seems a bit incongruous. How could a hydrogel with "enhanced" biocompatibility not be "biocompatible"?

presume that the recited methods utilizing certain biocompatible precursors will result in a biocompatible composition/hydrogel. The Court thus agrees with Defendant that its proposal is supported by the claim language and the intrinsic record. Therefore, the Court recommends that the "biocompatible" claim terms found in the respective claims, (*see supra* nn. 1-2), be construed to mean "a hydrogel/composition formed from crosslinked biocompatible precursors [as set out in the claim]."[9]

14. This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. Any objections to this Report and Recommendation should be filed by **April 2, 2018**; any responses should be filed by **April 6, 2018**. The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the district court. *See Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987); *Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006). The parties are directed to the Court's Standing Order for Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the District Court's website, located at http://www.ded.uscourts.gov.

15. Because this Report and Recommendation may contain confidential information, it has been released under seal, pending review by the parties to allow them to submit a single, jointly proposed, redacted version (if necessary) of the Report and Recommendation. Any such

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[9] Defendant also argues in its opening supplemental brief that the testimony of Plaintiffs' experts Dr. Jimmy Mays and Dr. Mark Distefano should be excluded because they lack relevant experience in the use and testing of polymer materials for medical applications. (D.I. 525 at 10) The Court does not agree that this requires the exclusion of their testimony. As Plaintiffs respond, an expert with a Ph.D. in the field of hydrogels may understand conclusions of biocompatibility based on the results of others, and it is permissible for an expert to rely on other experts to supplement knowledge in a particular area. (D.I. 544 at 2-3)

redacted version shall be submitted no later than **April 2, 2018** for review by the Court, along with a motion for redaction that includes a clear, factually-detailed explanation as to why disclosure of any proposed redacted material would "work a clearly defined and serious injury to the party seeking closure." *Pansy v. Borough of Stroudsburg*, 23 F.3d 772, 786 (3d Cir. 1994) (internal quotation marks and citation omitted). The Court will subsequently issue a publicly-available version of its Report and Recommendation.

Dated: March 27, 2018

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE