INTELLECTUAL PROPERTY ISSUES ASSOCIATED WITH BIOREPOSITORIES: CURRENT PRACTICES

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I. INTRODUCTION

As technological innovation over the last 20 years has offered ever more opportunity for the development of diagnostic and therapeutic inventions at the genomic and proteomic level, the leading edge of medical research today is increasingly found slicing through large collections of biospecimens held in government, university and private repositories. Specimens are collected from a variety of human sources for a particular purpose and then stored for future research and study. Beyond the ethical and regulatory considerations that are rich with conflicting public interests, the determination of who owns the potentially valuable intellectual property rights must be weighed against the unfettered need to promote further research and innovation that follows from data sharing and timely disclosure of results and inventions. With that in mind, what are the current practices regarding the disposition of intellectual property rights, or economic interests therein, that arise out of the study of human tissue specimens held in biorepositories and the use of the biologic information each of those specimens contains?

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II. BIOREPOSITORIES

It is conservatively estimated that, in the U.S. alone, there are over 300 million human tissue specimens stored in a large number of facilities ranging from formal repositories holding as many as 92 million specimens to the informal storage of blood or tissue in a researcher's freezer holding as few as 200 specimens.[1] The volume of biological materials in storage is increasing by 20 million units a year.[2] While such facilities are often also denominated as "tissue repositories", "biobanks", "registries", "libraries," and "genetic databases", the distinctions[3] are subtle, and here they will be collectively referred to as "biorepositories."

Biorepositories are maintained by institutions of government, academia and private industry. They include military facilities, sponsored facilities of the National Institutes of Health (the "NIH"), other federal agencies, state agencies such as forensic DNA banks and newborn screening laboratories, diagnostic pathology laboratories, university and research hospitals, commercial entities and non-profit organizations. The largest biorepository is the Armed Forces Institute of Pathology and Joint Pathology Center with specimens that have been collected for over 150 years.[4] The pathology departments at academic medical centers and community hospitals collectively constitute the largest and some of the oldest stores of biospecimens in the United State, some of which are over 100 years old.[5] Private sector collections

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[1] Eiseman et al. *Human Tissue Repositories "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era*, RAND SCIENCE AND TECHNOLOGY, 2003, *available at* http://www.rand.org/pubs/monograph_reports/MR954.html.

[2] Eiseman & Haga, *Handbook of Human Tissue Sources,* RAND SCIENCE AND TECHNOLOGY, 1999, *available at* http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA373679.

[3] *See, e.g.*, A. Cambon-Thomsen et al., *Trends In Ethical and Legal Frameworks For The Use of Human Biobanks,* EUROPEAN RESPIRATORY JOURNAL, 2007, *available at* http://www.ersj.org.uk/content/30/2/373.full.pdf+html.

[4] Eiseman et al., s*upra* note 1.

[5] Eiseman et al., s*upra* note 1.

are maintained for proprietary use as well as for distribution. Virtually every university medical center has created and maintains one or more biorepositories for research purposes under the supervision of the Institutional Review Board of that institution.[6]

III. SPECIMENS

Generally, the human tissue specimens[7] held in a biorepository are available for research purposes both within the institution maintaining the biorepository and for distribution to other researchers pursuant to a material transfer agreement ("MTA"). With advances in molecular biology, genetics, and informatics, there is less reliance on snap-frozen tissue, paraffin blocks or formalin-fixed tissue in preference for electronic databases of analyses of the tissues that is sufficient for the study of protein, gene expression and genetic somatic mutations. As a result, data regarding the actual physical tissue samples are increasingly transferred to researchers rather than the specimens from which the relevant data have been extracted and reduced to electronic storage media held and maintained by the

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[6] Eiseman & Haga, *supra* note 2.

[7] A human tissue specimen is broadly defined as:

> A quantity of tissue, blood, urine, or other biologically derived material used for diagnosis and analysis. A single biopsy may generate several specimens, including multiple paraffin blocks or frozen specimens. A specimen can include everything from subcellular structures (DNA) to cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, and placenta).

National Cancer Institute, *Glossary*, http://biospecimens.cancer.gov/aaBackup/cahub/news/index4837.html (last updated July 11, 2013).

biorepository.[8] For purposes of this discussion, any reference to human tissue specimens necessarily includes any data about such specimens retained by the biorepository.

Sources of such specimens are volunteers, clinical research protocols, autopsies, biopsies, blood, organ, sperm and embryo banks, pathology laboratories, and forensic laboratories. The most common source of tissue is from patients following diagnostic or therapeutic procedures.[9] The tissue specimens are stored by the biorepository for a variety of purposes, based upon its founding requirements, to fulfill a specific set of objectives including establishing correlations with respect to changes of structure and appearance of a tissue with a diagnosis of a disease and in longitudinal studies. Invariably, tissue specimens are maintained for uses that are unrelated to any original therapeutic or diagnostic purpose. For example, in describing the purpose of maintaining its biorepositories, the NCI[10] states that "commonly, human biospecimens are used to identify and validate ways to deliver drugs or agents to specific cells, identify how diseases progress and vary, group patients as more or less likely to respond to specific drugs, group patients to determine which treatment is

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[8] Most repositories collect pathology data about each specimen including demographic and diagnostic information. Some also try to collect medical history and clinical outcomes data. Eiseman et al., s*upra* note 1, at 48.

[9] Eiseman and Haga, *supra* note 2, at xviii. *See also* Childress et al. *Future Uses of the Department of Defense Joint Pathology Center Biorepository,* THE NATIONAL ACADEMIES PRESS 2010*,* at 37-64, *available at* http://www.nap.edu/openbook.php?record_id=13443&page=37.

[10] The National Cancer Institute ("NCI"), part of the NIH, which, in turn, is one of eleven agencies of the U.S. Department of Health and Human Services, supports several major tissue resources that provide support for research in early detection, breast and ovarian cancer, colorectal cancer, prostate cancer, pediatric oncology and many other disease-specific collections such as HIV/AIDS. The NCI is the largest of the NIH's biomedical research institutes. Other agencies within the NIH support a multitude of biorepositories in areas related to aging, allergies, heart and lung diseases, diabetes, brain studies, deafness and other communication disorders, and environmental-related studies.

appropriate and develop screening tests to detect biomarkers that are associated with certain stages or sub-types of a disease."[11]

IV. ETHICS AND INTERNATIONAL DIFFERENCES

Apart from a multitude of vexing and contentious ethical and regulatory issues that date back to the notorious U.S. Public Health Service syphilis study at Tuskegee, the Jewish Chronic Disease Hospital case, the Willowbrook hepatitis study and other such events in the US,[12] the issues of informed consent and confidentiality are a trenchant part of the historical development regarding the use of biological materials in research. Not surprisingly, these issues are international in scope and affect the grant of patent rights to discoveries in widely differing ways around the world.[13]

For example, under the European Union Biotechnology Directive and the European Patent Convention, there are exclusions for the awarding of patent rights to inventions that are contrary to "ordre public" or morality,[14] and, as a result, moral

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[11] National Cancer Institute, *Frequently Asked Questions,* http://biospecimens.cancer.gov/patientcorner/faq.asp#q3 (last visited February 13, 2014).

[12] *See* J. Katz, *Experimentation With Human Beings*, RUSSELL SAGE FOUNDATION, 1972.

[13] *See* Astrid Burhöi, *Moral Exclusions in European Biotechnology Patent Law*, LUND UNIVERSITY, 2006, http://lup.lub.lu.se/luur/download?func=downloadFile&recordOId=1337961&fileOId=1646263 (last visited February 13, 2014) and Thambisetty, *Ethics and Law of Intellectual Property*, ASHGATE PUBLISHING, 2007, *available at* http://tinyurl.com/njc7fj9.

[14] European Patent Convention, 14th Ed. 2010, art. 53(a) *available at* http://tinyurl.com/c6bmeth.

> European patents shall not be granted in respect of:
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> (a) inventions the publication or exploitation of which would be contrary to "ordre public" or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States

issues are to be considered in the biotechnology patent field. Since, in the EU system, case law is suggestive, but not determinative, each patent application must be determined on its own merits. To complicate matters further, the ability to obtain IP protection outside the US requires filing a patent application prior to public disclosure of research results through publication.[15] In the US, researchers have a period of one year to file a patent application from the point their data and results are disclosed.[16] Since the NIH 2003 data sharing policy regarding the use of biospecimens requires that "research and resources should be made

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Council Directive 98/44, art. 6, 1998, O.J.(L 213)

> 1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.
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> 2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
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> (a) processes for cloning human beings;
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> (b) processes for modifying the germ line genetic identity of human beings;
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> (c) uses of human embryos for industrial or commercial purposes;
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> (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

[15] European Patent Convention 1973, *Id.* at art 54(1) and 54(2).

> (1) An invention shall be considered to be new if it does not form part of the state of the art.
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> (2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

[16] 35 U.S.C. § 102.

available no later than acceptance for publication,"[17] these international differences intersect and collide with the intellectual property interests of those putative claimants otherwise entitled to exploit the rights.

V. POTENTIAL CLAIMANTS TO SPECIMEN OWNERSHIP AND INTELLECTUAL PROPERTY RIGHTS

Among those who have an arguable potential claim to property rights associated with tissue specimens in biorepositories are the biorepositories themselves, individual contributing researchers, academic and medical research institutions, industry sponsors of research, the United States government and the individual contributors of the specimens. These issues have been fiercely contested among several of these potential claimants, both in court and in contract negotiations.

One well-known such contest was *Moore v. Regents of University of California*[18] in which a patient who was treated for leukemia at a university medical center asserted that the cells of his removed spleen were economically valuable to his physician in the physician's research activities apart from the patient's leukemia treatment. The patient alleged conversion of those valuable cells, and the California Supreme Court determined that the tort of conversion could not apply to excised cells, and that the patient did not own a proprietary interest in the potentially lucrative cell line generated from his cells.[19]

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[17] http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm#time (last updated February 9, 2012).

[18] Moore v. Regents of University of California, 51 Cal. 3d 120 (1990), *cert. denied*, 499 U.S. 936 (1991).

[19] *Id.* at 137.

> Since Moore clearly did not expect to retain possession of his cells following their removal, to sue for their conversion he must have retained an ownership interest in them. But there are several reasons to doubt that he did retain any such

Building upon the logic in *Moore*, the court in *Greenberg v. Miami Children's Hosp. Research Inst.*[20] held that organizers, financial supporters and contributors to a tissue repository, the purpose of which was to find a treatment for a rare genetic disorder, owned no economic interest in the researcher's and the research institution's commercialization of the invention arising from their research on the tissue samples that they used to isolate the gene causing the genetic disease. The plaintiffs alleged that they had a property interest in their body tissue and genetic information. The court disagreed and declined to "find a property interest for the body tissue and genetic information voluntarily given to Defendants. These were donations to research without any contemporaneous expectations of return of the body tissue and genetic samples, and thus conversion does not lie as a cause of action."[21] The court found that the plaintiff donors had no cognizable property interest in body tissue and genetic matter donated for medical research.[22]

The most well-known of the legal contests between potential claimants to proprietary rights in biorepository tissue samples is *Washington University v. Catalona*[23] which resolved the matter, as between the researcher and the university medical center, which party owns the biorepository inventory of specimens. Dr. Catalona, a researcher and urologist at Washington University

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> interest. First, no reported judicial decision supports Moore's claim, either directly or by close analogy. Second, California statutory law drastically limits any continuing interest of a patient in excised cells. Third, the subject matters of the Regents' patent -- the patented cell line and the products derived from it -- cannot be Moore's property.

[20] Greenberg v.Miami Children's Hosp. Research Inst., 264 F. Supp. 2d 1064 (S.D. FL 2003)

[21] *Id.* at 1074.

[22] "[T]he property right in blood and tissue samples also evaporates once the sample is voluntarily given to a third party." *Id.* at 1075.

[23] Washington University v. Catalona, 437 F. Supp. 2d. 985 (2006), 490 F.3d 667, 673-77 (8th Cir. 2007), *cert. denied*, 128 S. Ct. 1122 (2008).

for over 25 years had been instrumental in establishing a biorepository for the collection and storage of biological specimens of prostate tissue, blood and DNA samples. More than 30,000 research participants were enrolled in prostate cancer research studies, in many of which Dr. Catalona was named as the principal investigator,[24] and about 3,000 of the participants had been patients of Dr. Catalona. The biorepository contained over 100,000 serum samples. Dr. Catalona left Washington University for a post at Northwestern University. He asserted the right to take the biorepository with him and demanded its transfer to Chicago. He also recruited a number of tissue donors to write letters to Washington University demanding the release of their tissue samples to Dr. Catalona. The court held that neither Dr. Catalona nor any of the tissue donors retained any property interest in the specimens in the biorepository and that Washington University retained all rights thereto.[25] In light of these case, as to tissue donors and the individual researchers and physicians who were instrumental in collecting the specimens, it is currently reasonably well-established that under common law property theories and state jurisprudence regarding gifts, they hold no proprietary interest in any inventions or discoveries that may be derived from a study of those specimens in a biorepository and the institution holding the repository owns the specimens.

What would be the claim of the United States Government? Since a very significant number of biorepositories are either supported by agencies of the US or owned by agencies of the US, the intellectual property rights that are derived from research using those resources are governed by technology transfer legislation.[26] The Bayh-Dole Act typically governs any demands for proprietary

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[24] See 21 C.F.R. § 312.3(b) (2013).

[25] "The Court finds that the RPs [research participants] had the present intent to donate their biological materials to WU to be maintained in the GU Repository. The informed consent forms repeatedly asserted WU's ownership of the donated materials and only listed Dr. Catalona as the Principal Investigator." *Id.* at 999.

[26] *See* 5 U.S.C. § 3710a and 35 U.S.C. § 200 *et seq.* Title II, Chapter 18, *Patent Rights in Inventions Made With Federal Assistance,* ("Bayh-Dole Act").

rights that would be asserted by the US. At most, the US retains a nonexclusive, nontransferrable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world.[27] In 1995, the NIH published the Uniform Biological Material Transfer Agreement[28] ("UBMTA") as a model agreement for general use in the exchange of biological materials between organizations involving biorepositories supported by NIH agencies. The disposition of intellectual property rights is covered in Section 8 of the UBMTA.[29] One treatment of intellectual property issues in an MTA with respect to a transfer of biological materials to a for-profit institution is reflected in the policies at the University of California Berkeley in which it is expected that any commercial use of research findings will require some sort of "consideration", presumably, a royalty payment, to the university.[30] Another approach to new inventions can be found in agreements such as with Vanderbilt University in which the university only requires a "non-exclusive license to use the same for non-commercial research, educational and patient care purposes."[31]

A more detailed discussion of the disposition of intellectual property rights in an MTA can be found in Section 8 of the Esophageal Adenocarcinoma and Barrett's Esophagus Consortium

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[27] 35 U.S.C. § 202(c)(4).

[28] 50 Fed. Reg. 45, 12771.

[29] *Id.* at 12774.

> The RECIPIENT is free to file patent application(s) claiming inventions made by the RECIPIENT through the use of the MATERIAL but agrees to notify the PROVIDE R upon filing a patent application claiming MODIFICATIONS or method(s) of manufacture or use(s) of the MATERIAL

[30] http://www.spo.berkeley.edu/guide/mtaquick.html (last visited February 13, 2014).

[31] *See* Level 5 MTA-Research Collaboration Agreement, http://www.vanderbilt.edu/cttc/mta (last visited February 13, 2014).

Agreement.[32] In general, intellectual property that is derived from a research project arising out of the use of the biorepository materials is to be owned by the participating member of the consortium except as otherwise provided in any agreement with a third party.[33] The result of this approach leaves the status of any intellectual property to be resolved in the same manner as such issues are typically resolved in clinical trial agreements between a sponsor and a research institution.[34]

VI. CLINICAL TRIAL AGREEMENTS

Classic tensions exist in the conduct of clinical human drug and device trials between the private pharmaceutical company or

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[32] *Esophageal Adenocarcinoma and Barrett's Esophagus Consortium Agreement*, 2005, http://www.docstoc.com/docs/26453617/ESOPHAGEAL-ADENOCARCINOMA-AND-BARRETTS-ESOPHAGUS-RESEARCH-CONSORTIUM (last visited February 13, 2014). The Esophageal Adenocarcinoma And Barrett's Esophagus Research Consortium is comprised of nine university medical centers including three Mayo Clinics. The Mayo Clinic Rochester is designated in the consortium agreement as the Host Institution. The consortium is supported by the NIH and its access policy with respect to the biological samples is regarded as a model by many. The consortium agreement has extensive detail regarding the disposition of intellectual property rights and licenses among its members.

[33] *Id.* at Section 8.3.1, page 12.

> *Research Project IP*. Subject to the provisions herein and to the terms and conditions of any applicable sponsored Research Project agreement, title to any Intellectual Property created during performance of the research Project shall remain with the inventing or creating Member Institution(s)

[34] *See also* International Cancer Genome Consortium Intellectual Property Policy, *available at* http://www.icgc.org/icgc/goals-structure-policies-guidelines/e4-intellectual-property-policy.

> All ICGC members agree not to make claims to possible IP derived from primary data (including somatic mutations) and to not pursue IP protections that would prevent or block access to or use of any element of ICGC data or conclusions drawn directly from those data.

device manufacturer, the investigational site, such as a university hospital, and the principal investigator at the site with respect to intellectual property issues. These conflicting interests are typically hammered out in the clinical trial agreement ("CTA") among the parties. In most situations, the principal investigator is not a party to the CTA, but, in a separate document, acknowledges his or her responsibilities and obligations as well as the disposition of the intellectual property rights.

From the perspective of the drug company or device manufacturer, the fully capitalized cost of a new drug or biopharmaceutical from preclinical research and development to market approval is $1.3 billion and $1.2 billion (in 2005 dollars) respectively, expended over a mean of five years.[35] Given that only one in five compounds makes it through to market approval from the filing with the United States Food and Drug Administration of an investigational new drug application,[36] industry sponsors of clinical trials have a very substantial interest in owning any rights to commercialize their inventions.

Similarly, research hospitals and their research staffs supply considerable expertise and investigative resources in identifying study subjects, and those institutions incur unreimbursed costs executing the clinical trial protocols and advancing and improving upon therapeutic modalities. In addition, the institution conducting the trial undertakes very substantial tort

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[35] DiMasi & Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?,* MANAGERIAL & DECISION ECONOMICS (2007), 28:469-479 *available at* http://emoglen.law.columbia.edu/twiki/pub/LawNetSoc/BahradSokhansanjFirstPaper/28ManageDecisEcon469_cost_of_biopharma_rd_2007.pdf. *Cf.* Sherer, *R&D Costs and Productivity in Pharmaceuticals,* HKS FACULTY RESEARCH WORKING PAPER SERIES, Harvard Kenned School of Government, 2011, *available at* https://research.hks.harvard.edu/publications/getFile.aspx?Id=745.

[36] DiMasi, *Risks in new drug development: approval success rates for investigational drugs*. CLINICAL PHARMACOLOGY & THERAPEUTICS, 2001;69:297-307 *available at* http://213.190.70.6/gmp.asso/Documents/Biblio/Risks%20in%20new%20drug%20development.pdf.

and contractual risks in deviating from generally recognized good clinical practices and standards of care[37] to follow the protocol in the study. If, in the course of a trial, the scientists at a research institution conceive or reduce to practice an invention that arises from their work in the trial or is developed by further research that has been suggested by study results, the study site has a legitimate interest in any commercialization of that invention. The industry sponsors, not unsurprisingly, take a different view.

These issues are heavily negotiated between the parties, and the outcome of those negotiations vary widely, but, presumably, a balanced resting place for the distribution of intellectual property rights arising from the study starts with the proposition that the separate ownership of any pre-existing intellectual property rights or other such rights developed independently of the study remain with respective parties. With respect to the study itself, there is usually significant conflict between the negotiating parties over the definition of any invention that arises, in some fashion, out of the study.

Typically, if the invention is conceived and reduced to practice by the researchers representing the institution, in direct performance of the study in accordance with the protocol, and that invention incorporates any confidential information or other proprietary information of the sponsor, the sponsor will be assigned that intellectual property. Often, such an assignment permits the research institution to retain a free nonsublicensable, nonexclusive license to practice that invention for internal noncommercial research and educational purposes.

If the invention is conceived or reduced to practice by the institution researchers independently of the confidential information or other proprietary information of the sponsor, the research institution would normally expect to retain any such intellectual property, often subject to the sponsor's option to

[37] U.S. Department of Health and Human Services, *National Guideline Clearinghouse, http://www.guideline.gov/browse/by-topic.aspx (last visited February 13, 2014).*

negotiate a separate agreement to acquire those rights or to receive a royalty. If the invention is jointly conceived by the parties during the study, then they would expect joint ownership on the same terms, generally.

VII. CONCLUSION

As current medical research continues to evolve relying increasingly upon sophisticated studies using human tissue specimens held in biorepositories, apart from the complexities in determining precisely what is a patentable invention[38] in this type of study, as between the potential claimants (the donors of specimens, the biorepositories, the researchers who collected the specimens, the research institutions, private sponsors and agencies of the United States government), the intellectual property (or economic interests in such intellectual property) derived from these studies is ultimately distributed among the downstream researchers pursuant to the vigorously negotiated terms of clinical trial agreements and material transfer agreements.

[38] *See* In re Bilski, 545 F.3d 943 (2008) (for purposes of biological research, implied a limitation on the availability for patents involving correlations between genetic or phenotypic attributes and treatment) *But cf.* Bilski v. Kappos, 130 S. Ct. 3218 (U.S. 2010) (the Court affirmed the decision of the Circuit Court in *In re Bilski* but held that the "machine-or-transformation" test is not the sole test for determining patent eligibility of a process). Correlation claims are a type of process claim. *Supra,* In re Bilski, at 1014.