

Commercializing Stem Cell-Based Therapies: Meeting NIH and FDA Requirements

by Kalah Auchincloss



In March, President Obama signed an executive order lifting the Bush Administration restrictions on federal funding for human embryonic stem cell (HES) research. The possibility of new federal funding opportunities, in combination with more than a decade of scientific advances in both embryonic and adult stem cell research, signal that stem cell-based therapies (“SCBT”) could soon be available for patients in a clinical setting. For those wishing to commercialize such therapies, it will be important to ascertain how the U.S. Food and Drug Administration (“FDA”), which has regulatory authority over U.S. marketing of SCBT, will exercise this oversight.

This article is not intended to be an exhaustive dissertation on all laws and regulations pertaining to stem cell research, embryonic or otherwise.¹ Rather, it discusses the controversial history of federal funding for stem cell research, and then focuses on regulations and guidelines likely to govern FDA approval of clinical applications of SCBT. It also discusses some of the recent recommendations included in the International Society for Stem Cell Research Guidelines in the context of U.S. application of those recommendations.

NIH: Restrictions on Federal Funding for Human Embryonic Stem Cell Research

Federal funding for human embryonic stem cell research enjoys a long and storied history, reflecting the moral, ethical, and political sensitivities of the U.S. Advances in the early 1990s eventually led to isolation of the first human embryonic stem cells in 1998. Anticipating the resulting public unease from those who believed an embryo was a human life, Congress passed the Dickey-Wicker amendment (named after its sponsors) in 1996. The amendment, which has been enacted annually as part of the appropriations process since 1996, prohibits the use of federal funding for any experiment in which a human embryo is either created for research purposes or “destroyed, discarded, or knowingly subjected to risk of injury or death...”² After passage of the amendment, an opinion from the Department of

¹ This article also does not address laws that exist in a number of states prohibiting certain forms of human embryonic stem cell research, somatic cell nuclear transfer, and/or cloning. See e.g., Az. Rev. Stat. §§ 32-3212, 35-196.04, 36-112, 36-2302, 36-2303.

² The Balanced Budget Down Payment Act, Pub. L. No. 104-99 § 104 (1996).

Health and Human Services (“HHS”) Office of the General Counsel interpreting the statutory language found that prohibiting the use of federal funds for human *embryo* research would not apply to research using embryonic *stem cells* “because such cells are not a human embryo within the statutory definition.”³ In accordance with the HHS opinion, the National Institutes of Health (“NIH”) indicated that it would not fund efforts to derive stem cells from human embryos (because this would destroy the embryo and run afoul of the law); but that it would fund research on the stem cells once they had been derived with private funding.

The NIH published guidelines to implement this policy, but before applications under the Clinton Administration guidelines were accepted and funded by the NIH, President Bush took office and issued a new HES research policy. Under that policy, federal funds could be (and have been) used for research on human embryonic stem cells where: the derivation process was initiated prior to 9 p.m. EDT August 9, 2001; the embryo was created for reproductive purposes; the embryo was no longer needed for these purposes; informed consent was obtained for the donation of the embryo; and no financial inducements were provided for donation of the embryo.⁴

President Bush’s policy was in effect until March 9, 2009, when President Obama signed Executive Order 13505 revoking the restrictions and directing the NIH to issue new guidelines to implement the new funding policy.⁵ According to the new NIH guidelines, which were finalized on July 7, 2009, the NIH will fund HES research “using only those human embryonic stem cells that were derived from embryos created by *in vitro* fertilization (IVF) for reproductive purposes and were no longer needed for that purpose.”⁶ These guidelines preserve President Bush’s

³ Letter from HHS Gen. Counsel Harriet Rabb to Harold Varmus, Director, NIH (Jan. 15, 1999).

⁴ President Bush Statement (Aug. 9, 2001), available at <http://usgovinfo.about.com/blwhrelease16.htm> and <http://stemcells.nih.gov/policy/2001policy.htm>; Executive Order 13435: *Expanding Approved Stem Cell Lines in Ethically Responsible Ways*, 72 Fed. Reg. 34591 (Jun. 22, 2007).

⁵ Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*, 74 Fed. Reg. 10668 (Mar. 11, 2009). In the Executive Order, the President permits the Secretary of HHS, through the Director of the NIH, to support and conduct “responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.” *Id.*

⁶ NIH, *Guidelines for Human Stem Cell Research*, 74 Fed. Reg. 32170 (Jul. 7, 2009).

precedent in permitting funding for certain HES research, but, by eliminating the Aug 9, 2001 date, adopt President Clinton's more expansive approach in determining what projects are eligible for funding. The NIH goes on to state that under the new guidelines, it will *not* fund research using human embryonic stem cells derived from other sources, "including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes."⁷

The new guidelines should provide additional opportunities for federal funding for HES research, and depending upon funding streams, could lead to exciting new scientific advances. Furthermore, while the Dickey-Wicker amendment is in force for fiscal year 2009, the President's Executive Order could be a signal to Congress to reconsider its position in subsequent fiscal years, opening the door for additional federal funding.

FDA: Oversight of Clinical Stem Cell Therapies

New sources of NIH funding for stem cell research and new scientific advances bring us closer to clinical applications of SCBT, including transferring or implanting stem cells into humans for therapeutic purposes, which is the focus of this article. As we move toward the clinical use of SCBT, FDA's role in oversight of products used in humans becomes important to understand.⁸

⁷ *Id.* The NIH received 49,000 comments to the draft guidelines, several of which argued that research on additional sources of human stem cells (e.g., embryos created for research purposes or by somatic cell nuclear transfer) should be eligible for NIH funding. In response, the NIH stated that "the Guidelines reflect the broad public support for federal funding of research using hESCs created from such embryos based on wide and diverse debate on the topic in Congress and elsewhere. The use of additional sources of human pluripotent stem cells proposed by the respondents involve complex ethical and scientific issues on which a similar consensus has not emerged. For example, the embryo-like entities created by parthenogenesis and SCNT require women to donate oocytes, a procedure that has health and ethical implications, including the health risk to the donor from the course of hormonal treatments needed to induce oocyte production." *Id.*

⁸ While this article does not focus in depth on preclinical or laboratory stem-cell based research, it is valuable to briefly note several applicable regulations. In addition to the restrictions on federal funding for human embryonic stem cell research, like other pre-clinical research, all stem cell research (both HES and adult stem cell research) may be subject to: protections for animals in research (e.g., the Public Health Service Act § 289d and the Animal Welfare Act, 7 U.S.C. § 2131 et seq.); FDA Good Laboratory Practice Regulations, 21 C.F.R. Part 58; privacy rules under the Health Information and Portability Accountability Act (HIPAA), Pub. L. No. 104-191 (1996); and oversight of recombinant DNA research under the NIH Guidelines for Research Involving Recombinant DNA Molecules, available at http://oba.od.nih.gov/oba/rac/guidelines_02/NIH_Gdlnes_Ink_2002z.pdf. The majority of these policies are applied to stem cell research much as they are applied to other forms of laboratory research.

Clinical Research: Human Subject Protections

Protections for human subjects are outlined in the Federal Policy for the Protection of Human Subjects, or the “Common Rule”, and apply to all research “involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency” which has adopted the Common Rule.⁹ The Common Rule also applies to research, whether or not funded by a government agency, performed at an institution which has agreed to abide by the provisions.¹⁰ Human subject protections require informed consent of human participants in the research, as well as approval and ongoing monitoring of the study by an Institutional Review Board (IRB).¹¹ Approval by an IRB can only be obtained if the IRB determines, among other things, that the risks to subjects are minimized and are reasonable in relation to anticipated benefits.¹²

For SCBT, this risk-benefit analysis could be particularly difficult, as transplantation of the product is permanent. Unlike other drugs which can be stopped at any time, implantation of stem cell based therapies cannot be undone and could lead to lasting adverse effects. This has implications for the risk-benefit calculation undertaken by the IRB, as well as consequences for obtaining informed consent from the study participant, who must fully understand the permanency of therapy. Moreover, an ethical calculation must also factor into the informed consent and IRB review process. The International Society for Stem Cell Research (ISSCR) recently recommended that “human subjects review of stem cell-based clinical protocols must enlist stem cell-specific scientific and ethical expertise.”¹³ In addition, the ISSCR recommends that clinical researchers “provide the utmost clarity regarding the potential benefits of participating in the trial with stem cells; since patients may have recourse to reasonable therapeutic alternatives, the informed consent process must emphasize the novel and experimental aspects of cell based interventions.”¹⁴

⁹ The Department of Health and Human Services has codified the Common Rule at 45 C.F.R. Part 46. Other federal agencies have codified the protections elsewhere in the Code of Federal Regulations. See also <http://www.hhs.gov/ohrp/humansubjects/guidance/basics.htm>.

¹⁰ HHS Office for Human Research Protections, *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles* (Mar. 19, 2002), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf>.

¹¹ 45 C.F.R. §§ 46.101, 46.111, 46.116 (2008).

¹² 45 C.F.R. § 46.111 (2008).

¹³ International Society for Stem Cell Research, *Guidelines for the Clinical Translation of Stem Cells, Recommendation 2* (Dec. 3, 2008), available at http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf [hereinafter ISSCR Guidelines].

¹⁴ *Id.* at Recommendation 3; see also Recommendations 20 and 28.

Clinical research to test a stem cell based therapy in humans which is funded by NIH grant money would certainly be subject to the Common Rule. Interestingly, whether human subject protections apply to laboratory research on human embryonic stem cell lines is a more difficult question to answer (and may become a more prominent issue with the opening of NIH funds for HES research). In general, HHS-conducted or supported research that does not involve living humans or identifiable private information is not considered human subjects research, and is thus not subject to human subject protections.¹⁵ Applying this to HES laboratory research, HHS guidelines indicate that if the investigator utilizes already established cell lines from which the identify of the donor(s) cannot be readily ascertained, then *in vitro* research and research in animals using those cell lines is not considered human subject research and is therefore not governed by human subject protection regulations or IRB oversight.¹⁶ In contrast, laboratory research on human cell lines where the donor may be identified would be subject to the Common Rule provisions.¹⁷ Investigators should carefully consider whether their stem cell laboratory research is subject to the Common Rule.

Clinical Research: HCT/P Regulations and FDA IND Requirements

Articles “containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient” are considered “human cells, tissues, and cellular and tissue-based products” (HCT/P) subject to FDA regulations.¹⁸ Most SCBT would fall into this category, assuming the product is intended to be transplanted into the recipient patient as part of the therapeutic intervention. In addition, stem-cell based products are almost certain to be regulated as biological products under the Public Health Service Act if they “are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes.”¹⁹

¹⁵ 45 C.F.R. § 46.102(f) (2008); see also HHS Office for Human Research Protections, *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles* (Mar. 19, 2002), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf>.

¹⁶ *Id.*

¹⁷ *Id.* Note also that informed consent from embryo donors for research on unused embryos is generally required by state property laws in all states, usually at the time of embryo donation.

¹⁸ 21 C.F.R. § 1271.3(d) (2009); see 42 U.S.C. § 264.

¹⁹ 21 C.F.R. § 1271.10 (2009); FDA, *Proposed Approach to Regulation of Cellular and Tissue Based Products*, 62 Fed. Reg. 9721 (Mar. 4, 1997), available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf>.

The HCT/P regulations are intended to prevent the introduction, transmission, or spread of communicable diseases. Accordingly, these regulations require the manufacturer of HCT/P to comply with good tissue practices, including donor screening and testing²⁰ and to register with FDA and list all HCT/P manufactured.²¹ Any institution or company which engages in a clinical trial of stem cell based therapies which are implanted into humans will need to comply with the HCT/P regulations.²² With SCBT, in addition to screening for infectious diseases as required by the FDA, it may also become important to screen the donor for genetic diseases, the risk of which could be passed on to the recipient. Although not required by the FDA HCT/P regulations, the ISSCR specifically recommends screening for genetic diseases, as appropriate, in addition to screening for infectious diseases.²³

Depending on how FDA construes “highly processed” or “used for other than their normal function,” most SCBT will likely also be subject to FDA premarket approval as a biological product under section 351 of the Public Health Service Act. In contrast to the HCT/P regulations which are intended to prevent contamination or transfer of communicable diseases; premarket approval provisions require the sponsor to demonstrate that the product is safe and effective for its intended use. For biological products, the sponsor must submit a Biologics License Application showing the biologic is safe, pure, and potent.²⁴

Moreover, if the stem cell product is considered a biological product, even before submitting data to support marketing approval of the therapy, the sponsor must submit an Investigational New Drug (IND) application to FDA for clearance to conduct human clinical trials with the product.²⁵ Such research is subject to FDA human subject protections and IRB regulations, in addition to applicable Common Rule requirements.²⁶ Again, the informed consent process and ongoing IRB

²⁰ 21 C.F.R. Part 1271, Subparts C and D (2009).

²¹ 21 C.F.R. Part 1271.10 (2009).

²² According to the regulations, “manufacturer” means, but is not limited to, “any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.” 21 C.F.R. § 1271.10(e).

²³ ISSCR Guidelines at Recommendation 4; see 21 C.F.R. § 1271.85.

²⁴ 42 U.S.C. § 262 *et seq.* (2009); 21 C.F.R. §§ 610.10, 610.11, 610.13, 600.3 (2009).

²⁵ 21 C.F.R. Part 312 (2009). Among other things, the IND application must include a commitment from the sponsor: (1) not to begin clinical investigations until an IND covering the investigations is in effect; (2) that an IRB will be responsible for the initial and continuing review and approval of the clinical study; and (3) to conduct the investigation in accordance with all other applicable regulatory requirements. *Id.*

²⁶ 21 C.F.R. Part 50 (2009); 21 C.F.R. Part 56 (2009).

oversight will be critical for stem cell based therapies – the ISSCR repeatedly emphasizes that ensuring study participants’ comprehension of all risks and benefits should be done at each phase of the clinical trial, and, ideally, would be “assessed through a written test or an oral quiz during the time of obtaining consent.”²⁷

In January 2009, FDA cleared the first IND for a human clinical trial using the product of human embryonic stem cell therapy.²⁸ Although the IND, submitted by Geron Corporation, was placed on “clinical hold” on August 18 to allow FDA to review additional animal study data, Geron has announced that it will continue to work with FDA to address the agency’s concerns, and is hopeful it will be able to proceed with the Phase I trial of GRNOPC1 to assess the safety of the therapy in patients with acute spinal cord injury.²⁹ If allowed to move forward, the GRNOPC1 trial will yield important scientific information regarding the safety and efficacy of the product.

The Geron IND will also be a useful regulatory model for subsequent SCBT. According to press releases, the initial 21,000 page IND underwent extensive FDA review, which was in part influenced by the ISSCR guidelines.³⁰ This may signal the importance of the ISCR recommendations in shaping the U.S. regulatory process. As such, it will be crucial for peer companies to closely monitor the Geron process to assess the type and quantity of data required by FDA, and the interaction between the agency and the sponsor. The ISSCR, for example, specifically recommends that “the level of regulation and oversight should be proportional to the degree of risk raised by the particular cell product and intended use.”³¹ This is consistent with FDA’s oversight of other medical products and will presumably be adopted by the FDA.

However, the ISSCR also recommends that “clinical research should compare new stem cell-based therapies against the best medical therapy currently available to the local population.”³² This approaches “comparative effectiveness research” and could prove more difficult to undertake, as the U.S. struggles with how to define and

²⁷ ISSCR at Recommendation 28.

²⁸ Geron Press Release (Jan. 23, 2009), available at <http://www.geron.com/grnopc1clearance/grnopc1-pr.html>.

²⁹ Geron Press Release (Aug. 18, 2009), available at <http://www.geron.com/media/pressview.aspx?id=1187>. According to Geron, GRNOPC1 is “a collection of oligodendrocyte precursor cells (OPC) that will be injected into the spinal cord of patients with spinal cord injuries.” Geron hopes that the injected OPCs will eventually mature to form myelin, the protective sheath that surrounds spinal neurons. This could help repair spinal injuries due to torn or damaged myelin (though it will not help patient whose injuries are due to torn or severed spinal neurons). *Id.*

³⁰ *Id.*

³¹ ISSCR Guidelines at Recommendation 8.

³² *Id.* at Recommendations 25 and 26.

fund such research.³³ That being said, the FDA increasingly requests superiority studies demonstrating that the new product is better than existing therapies in terms of patient outcomes, patient quality of life, safety profile or some other definable measure.³⁴ Whether the FDA will require comparative effectiveness or superiority data for SCBT is an open question.

In addition to the ethical considerations which factor into the informed consent process for human subjects who participate in stem cell based clinical research, the ISSCR recommends that “regulatory and oversight agencies (local, national and international) must explicitly include the consideration of social justice principles into their evaluations. Mechanisms include (a) involvement of community and patient advocates in public discussions, committee representation, and oversight board evaluation procedures; (b) opportunity for open discussions about ethical issues; (c) enforcement of social justice considerations by appropriate agencies.”³⁵ In keeping with the FDA’s recent transparency initiative³⁶, FDA may convene public meetings to discuss the ethical implications of stem cell based therapies, and may even explicitly consider such factors into the approval decision, though how the agency will do so is not clear.

Finally, Geron Corporation utilized the “pre-IND” process to engage with FDA prior to submission of the IND and to work with the agency to discuss what information would be needed to support the IND application.³⁷ The pre-IND process is routinely used by pharmaceutical and biotech companies and could be particularly useful to sponsors of INDs for stem cell based therapies, in addition to frequent interaction between the agency and the sponsor after submission of the IND.

³³ The debate on comparative effectiveness research (CER) in the U.S. has focused on the methodology to be employed (literature reviews, head-to-head randomized controlled clinical trials, inclusion of cost as a factor, sampling of appropriate and varied patient populations), what federal (or non-federal) agency or entity should oversee such research, and permissible uses for information generated by such research (e.g., whether it may be used by payors to determine coverage decisions). See e.g., J. Avorn, *Debate about Funding Comparative-Effectiveness Research*, *N Engl J Med.* 7;360(19):1927-9 (May 2009); S. 1213, Patient-Centered Outcomes Research Act of 2009, introduced by Senators Max Baucus (D-MT) and Kent Conrad (D-ND), June 9, 2009.

³⁴ See FDA, *Draft Guidance for Industry Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval* (Oct. 2007), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070951.pdf>.

³⁵ ISSCR Guidelines at Recommendation 35.

³⁶ Notice of Transparency Task Force Public Meeting, 74 Fed. Reg. 26712 (Jun. 3, 2009); see also <http://www.fda.gov/AboutFDA/WhatWeDo/FDATransparencyTaskForce/default.htm>.

³⁷ Geron Press Release, *supra* note 29.

Post-Market Surveillance

Even after FDA approval of a stem cell based therapy for clinical use, unexpected adverse events may still emerge as a more diverse patient population uses the product. Although still years in the future, to manage ongoing safety concerns related to approved clinical uses of SCBT, the FDA may heavily utilize its postmarket authorities. In the 2007 Food and Drug Administration Amendments Act (FDAAA) FDA was given two new authorities which may be particularly relevant to stem cell based therapies, assuming such therapies are approved as biological products.

Under FDAAA, to ensure “the benefits of the drug outweigh the risks of the drug,” FDA may require a Risk Evaluation and Mitigation Strategy (REMS), which must be reassessed at specific intervals, and may include a Medication Guide or patient package insert, a communication plan for outreach to healthcare providers; and even restrictions on distribution or use of the drug.³⁸ Most REMS for approved drugs include only the timetable for assessment and the less burdensome requirements, such as a Medication Guide. However, the FDA has exercised its authority to restrict distribution and use of the drug. For example, the REMS for Entereg restricts the drug to inpatient use only and requires that hospitals be specially certified before dispensing the product.³⁹ FDA has also imposed a REMS on an entire class of drugs, opioids, which could include restrictions on use.⁴⁰ Given the long term safety concerns and relative novelty of SCBT, FDA may require a REMS for any single approved stem cell based therapy. The REMS would likely include at least a Medication Guide, and perhaps even certain restrictions on the distribution or use of the therapy (e.g., restrictions on who may administer the therapy and in what healthcare settings). A class-wide REMS applied to all SCBT, rather than determined on a case-by-case basis, is also possible, though perhaps in the more distant future.

In addition to REMS, FDA may require a Phase IV postmarket safety study, pursuant to the authority for such outlined in FDAAA. Under FDAAA, FDA may require a postmarket safety study for a new drug or biologic based on “appropriate scientific

³⁸ Food and Drug Administration Amendments Act of 2007, Pub. Law 110-85 § 901 (Sept. 27, 2007), *codified at* 21 U.S.C. § 355-l.

³⁹ FDA Press Release, *FDA Approves Entereg to Help Restore Bowel Function Following Surgery* (May 20, 2008), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116899.htm>.

⁴⁰ FDA, *Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs*, Notice of Public Meeting, 74 Fed. Reg. 17967 (Apr. 20, 2009); see also <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

data” to evaluate a known risk of the product, assess a signal of serious risk of the drug, or to identify an unexpected serious risk if data indicate there is potential for such a risk.⁴¹ The trial may only be required if adverse event reporting and active postmarket surveillance are not sufficient to manage and detect adverse events. Moreover, although FDA has long requested Phase IV studies, FDAAA includes a new enforcement mechanism by permitting imposition of civil monetary penalties if a postmarket safety study is required, but the sponsor does not complete the trial.⁴² The FDA could elect to require a post-market safety study for a SCBT, if the agency determines, based on the particular product, that other postmarket authorities are not sufficient to detect safety concerns (and provided a sufficient patient population for the trial is available).

Conclusion

With the availability of new federal money for HES research, and the first IND close to being cleared for clinical studies of a SCBT, we are inching toward the day when SCBTs are FDA-approved for clinical indications. For those who engage in clinical stem cell research and are looking ahead to eventual FDA approval, it will be important to assess how FDA will apply current authorities to stem cell based products, what modifications to these authorities will be required, and whether new authorities will be necessary. Close monitoring of Geron Corporation’s GRNOPC1 will be informative, both from a scientific and regulatory perspective. It will also be important to examine the ISSCR Guidelines to assess whether and how FDA should implement the ISSCR recommendations.

⁴¹ 21 U.S.C. § 355(o)(3).

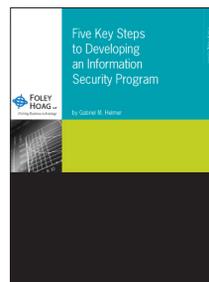
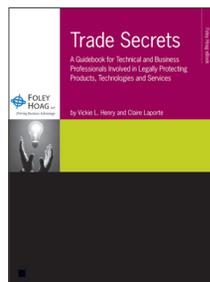
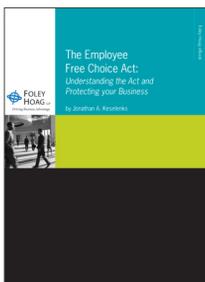
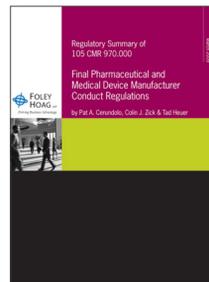
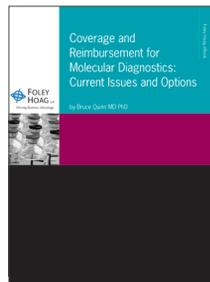
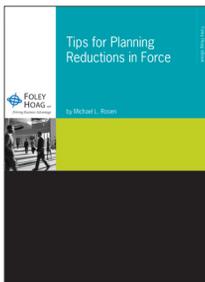
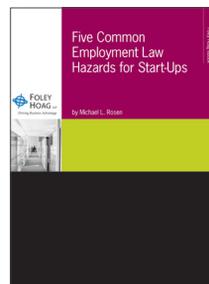
⁴² *Id.*

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