ARTICLES

HOW TO INTEGRATE ADMINISTRATIVE LAW AND TORT LAW: THE REGULATION OF STEM CELL PRODUCTS

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TABLE OF CONTENTS

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INTRODUCTION

Current administrative law is ill-prepared to deal with the surge of stem cell products poised to enter the market in coming years. The risks and rewards of such products differ markedly from those associated with drugs, medical devices, other biological products, and combination products. The differences necessitate a revamping of administrative law and the creation of a specialized regime of product liability. This Article proposes changes in administrative regulations to account for the special characteristics of stem cell products. These changes will promote the safety and effectiveness of stem cell products and reduce barriers to entry for stem cell makers. Simultaneously, this Article takes into account the justifications for altering the product-liability regime, which I discuss in a companion article on stem cell product liability.[1]

Stem cell products have the potential for enormous good and enormous harm. Yet, because of a radical lack of information, it is now nearly impossible to separate beneficial products from harmful ones. The unpredictability of risk and reward with stem cell products calls for an

1. *See generally* Stephen R. Munzer, *Risk and Reward in Stem Cell Products: A New Model for Stem Cell Product Liability*, 18 B.U. J. SCI. & TECH. L. 102 (2012) (challenging the typical economic assumptions underlying product liability law in constructing a product liability regime for stem cell products).

aggressive role by the Food and Drug Administration (FDA). The FDA ought to decide, in a manner that does not hinder innovation, which products should be allowed on the market and with what instructions, warnings, and restrictions on use. I contend that the Center for Biologics Evaluation and Research (CBER) is the best FDA center to assess the safety and effectiveness of stem cell products.

Some might object that this Article is premature because few stem cell products are now on the market. However, given the pace of technological advance in the biological sciences, an eventual flood of stem cell products seems inevitable. It would be foolish to wait until we have a decade of experience and large numbers of stem cell products before making any administrative adjustments. It is far more sensible to discern in advance, insofar as it is possible, the probable nature of the risks associated with stem cell products and to design a regulatory system for responding appropriately to these risks.[2] This is a job for today, not for a decade hence when legal and policy analysts can do little more than play catch-up. Thus, I concentrate here on upstream rather than downstream regulatory precautions.[3] However, my regulatory proposal is dynamic in that it allows for adjustment over time in light of new information.[4] This dynamism prevents my proposal from snuffing out innovative new stem cell products.

The regulatory scheme I propose suggests, first, that to acquire more and

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2. The Food and Drug Administration (FDA) approved a stem cell product known as Hemacord on November 10, 2011. *November 10, 2011 Approval Letter—Hemacord*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm279613.htm (last updated Nov. 10, 2011). Anyone who clicks on the Package Insert on the website will see that the warnings are substantial. Less than a year later, the FDA approved another stem cell product. *See May 24, 2012 Approval Letter—HPC, Cord Blood*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm305620.htm (last updated May 25, 2012) (approving HPC, cord blood). Canada has approved Prochymal, a mesenchymal stem cell product used to treat children with graft-versus-host disease (GVHD) and perhaps other ailments. Andrew Pollack, *A Stem-Cell-Based Drug Gets Approval in Canada*, N.Y. TIMES, May 17, 2012, http://www.nytimes.com/2012/05/18/health/a-stem-cell-based-drug-gets-approval-in-canada.html.

3. The language of upstream versus downstream precautions comes from Carl F. Cranor, *Protecting Early Warners and Late Victims in a Precautionary World*, *in* EUROPEAN ENVIRONMENTAL AGENCY, LATE LESSONS FROM EARLY WARNINGS 2 (Copenhagen, European Environmental Agency) (in press) (page proofs obtained June 17, 2012) (forthcoming 2012). I use these terms a bit differently than Cranor.

4. *See infra* text accompanying note 116 (contending that such a dynamic approach would encourage advances in stem cell products). The plain fact that these issues involve uncertainty and the future poses special difficulties. *See generally* Louis Kaplow & David Weisbach, *Discount Rates, Social Judgments, Individuals' Risk Preferences, and Uncertainty*, 42 J. RISK & UNCERTAINTY 125 (2011) (identifying analytical problems in other economic models typically used for evaluating policies whose benefits and costs extend into the future).

better information, the FDA should strengthen preapproval requirements and preclinical administrative review. Second, the FDA ought to monitor both the short-term and long-term performance of stem cell products. For this to work, the FDA must improve its record of monitoring post-market drug safety. Third, the FDA ought to devise a risk-management and risk-reduction system that relies far more on the gathering of information than previous regulatory systems. Finally, the most ambitious feature of my regulatory proposal integrates the regulatory scheme effectively with the best liability system for defective stem cell products. To be most efficacious, the interlocking regulatory and product liability elements must satisfy three criteria: complementarity, well-suitedness, and mutual reinforcement. These criteria, which are semi-technical in ways to be explained in Part VI.A, are fundamental to extending the regulatory regime, advocated here for stem cell products, to other areas where administrative law and tort law intersect, such as nanotechnology and toxic substances.

The Article takes the following course. After Part I explains stem cell products, Part II sketches the FDA process and shows why its classificatory system matters. Part III argues that sui generis regulation is unwise and ferrets out some useful points from the academic literature. Part IV maps out and defends the proposed regulatory scheme. Part V distills the main lines of the product liability regime that I advance elsewhere.[5] Part VI then shows that the regulatory proposal and the liability regime are complementary, well-suited, and mutually reinforcing, and demarcates the extent to which this integration of tort and administrative law can be generalized to nanotechnology and toxic substances.

I. SOME FUNDAMENTALS OF STEM CELLS AND STEM CELL PRODUCTS

All the cells of an individual human being derive from a zygote—the product of the fertilization of an egg by a sperm cell.[6] As the cells of the organism divide, the zygote develops into a blastocyst, then an embryo, and eventually into a fetus.[7] A common functional definition of a stem cell is that it is any cell that has the capacity to self-renew and to differentiate into

5. *See* Munzer, *supra* note 1, at 135–49 (detailing the possible implementation of the proposed product liability regime in different types of suits and under schemes that determine the scope of liability among multiple manufacturers).

6. Although nonhuman animals have stem cells, this Article is entirely concerned with human stem cells and products made from them.

7. The term "embryo" is sometimes used to encompass all stages of development before the fetus. *See* CHRISTOPHER THOMAS SCOTT, STEM CELL NOW: FROM THE EXPERIMENT THAT SHOOK THE WORLD TO THE NEW POLITICS OF LIFE 27 (2006) (presenting the zygote, morula, and blastocyst as specific examples of pre-fetal developmental forms that are classified as embryos).

a more committed cell.[8] Human embryonic stem cells (hESCs) begin either wholly undifferentiated or nearly so. As the embryo develops, its cells self-renew into other hESCs, become more differentiated cells, or divide into one hESC and one more differentiated cell.[9] As these changes occur, most cells become increasingly restricted in function and eventually develop into fully specialized cells, such as brain cells and red blood cells.[10] Fully specialized cells cannot replicate themselves indefinitely. Ultimately, they age and in time can no longer divide.[11]

The chief purpose of practically oriented stem cell research is to develop stem cell lines that are therapeutically useful. The stem cells used for research and medical purposes often originate from embryos. But somewhat more differentiated stem cells also exist in fetal and adult tissues.[12] The most common sort of fetal and adult stem cells used in medical practice are hematopoietic stem cells—stem cells that can differentiate into lymphoid cells and different sorts of blood cells.[13] Whether fetal and adult stem cells can be given the same, or roughly the same, therapeutic potential as embryonic stem cells (ESCs) is a matter of scientific debate.[14] Ethical issues also influence the availability and use of each type of stem cell tissue.[15] Despite fierce disagreements on ethical

8. Douglas A. Melton & Chad Cowen, *"Stemness": Definitions, Criteria, and Standards*, *in* ESSENTIALS OF STEM CELL BIOLOGY xxiii, xxiii (Robert Lanza et al. eds., 2d ed. 2009).

9. *See* T. Ahsan et al., *Stem Cell Research*, *in* PRINCIPLES OF REGENERATIVE MEDICINE 28, 29 (Anthony Atala et al. eds., 2008) (noting that stem cells can become precursor cells whose division yields fully differentiated cells at an exponential rate and thereby enhances the capability of cell-based treatments).

10. *See id.* (underscoring that adult stem cells differentiate into fewer cell types than other stem cells).

11. ALICE PARK, THE STEM CELL HOPE: HOW STEM CELL MEDICINE CAN CHANGE OUR LIVES x (2011).

12. Examples include multipotent adult progenitor cells, bone marrow stem cells, neural stem cells, mesenchymal stem cells, hepatic stem cells, skeletal muscle stem cells, and pancreatic stem cells. PRINCIPLES OF REGENERATIVE MEDICINE, *supra* note 9, at 258–83, 300–417.

13. *See* Stephen R. Munzer, *The Special Case of Property Rights in Umbilical Cord Blood for Transplantation*, 51 RUTGERS L. REV. 493, 500 (1999).

14. *See* Ahsan et al., *supra* note 9, at 34. Although adult stem cells appear to be limited in function, it is disputed whether these cells may be more flexible than previously thought. *See id.* (emphasizing that scientific exploration of the plasticity of stem cells and the qualities of stem cells in adult animals may indicate that adult human stem cells have a greater capacity to become more specialized than has been shown to date). Additionally, adult stem cells are often harder to isolate and transplant. *See id.* at 32–33 (observing that even bone marrow and blood provide few usable stem cells, though such cells are among the easiest stem cells to isolate).

15. Scholarship abounds on the ethical issues surrounding stem cell use. *See, e.g.*, MICHAEL BELLOMO, THE STEM CELL DIVIDE: THE FACTS, THE FICTION, AND THE FEAR

issues, interest in inducing fully differentiated somatic cells to become pluripotent stem cells (iPSCs) has increased sharply within the last six or seven years.[16]

Once stem cells are isolated from a particular source, the cells may be guided to self-renew in large numbers and thereby produce what is known as a stem cell line.[17] A stem cell line is indispensable to the creation of therapies and products. Stem cell products, which can help to create tissues and organs, hold hope for treating a wide range of conditions—from cancer to osteoarthritis to heart disease, among many others.[18] In addition to stem cells and stem cell lines, some medical treatments rely on combinations of stem cells and devices. The devices are typically used to place the stem cells into the body at the treatment site.[19]

II. CURRENT ADMINISTRATIVE LAW AND STEM CELL PRODUCTS

A central purpose of administrative regulation in this field is to make sure that stem cell products are competently evaluated, for both safety and effectiveness, by the best-suited center within the FDA bureaucracy. The FDA must accomplish this goal without extinguishing innovation in the regulated field. Since existing FDA practices do not always achieve this balance, improvement is needed.

Under current law, a manufacturer must follow a strict protocol to get its

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DRIVING THE GREATEST SCIENTIFIC, POLITICAL, AND RELIGIOUS DEBATE OF OUR TIME (2006) (tracing the historical development and the possible future trajectories of stem cell research); FUNDAMENTALS OF THE STEM CELL DEBATE: THE SCIENTIFIC, RELIGIOUS, ETHICAL, AND POLITICAL ISSUES 62–78, 146–96 (Kristen Renwick Monroe et al. eds., 2008) (containing articles by Philip J. Nickel and Ronald B. Miller that discuss the possible legal, ethical, and societal foundations for conducting research on human embryos); LEO FURCHT & WILLIAM HOFFMAN, THE STEM CELL DILEMMA: BEACONS OF HOPE OR HARBINGERS OF DOOM? (2008) (assessing the potential of stem cell research to provide treatments for several diseases); ROBERT P. GEORGE & CHRISTOPHER TOLLEFSEN, EMBRYO: A DEFENSE OF HUMAN LIFE (2008) (addressing four objections to the proposition that human embryos deserve moral respect to the extent given to fully developed human beings).

16. *See, e.g.*, Shinya Yamanaka, *A New Path: Induced Pluripotent Stem Cells*, *in* ESSENTIALS OF STEM CELL BIOLOGY, *supra* note 8, at xxi–xxii (recognizing that scientists have been able to induce pluripotent stem cells (iPSCs) in both mice and humans through the use of the same transcription factors).

17. *See* BELLOMO, *supra* note 15, at 58–59 (describing an actual experiment that involved growing cells for easy testing for and preservation of pluripotency and produced five lines of stem cells).

18. *See* Mikkel L. Sorensen, *Preface* to STEM CELL APPLICATIONS IN DISEASES vii, vii (Mikkel L. Sorensen ed., 2008) (analogizing stem cells to microchips that one can tailor to complete specific functions).

19. See PRINCIPLES OF REGENERATIVE MEDICINE, *supra* note 9, at 579–1332, for a wide-ranging discussion of the biomaterials needed for cell and tissue therapeutic products.

product to market. First, the maker must fill out the appropriate application.[20] Next, it sends the application to a center within the FDA.[21] Then, the manufacturer seeks approval to market the stem cell product. Approval depends on satisfying the FDA on two key points: safety and effectiveness.[22] Evidence on both points usually comes first from animal studies and later from human trials. Only after the maker demonstrates the safety and effectiveness of a particular product in animals may it begin clinical trials for its safety and effectiveness in humans. Eventual approval hinges on three ever-widening phases of clinical trials in humans. The maker must also show that it can supply the item in consistent batches,

20. In this context, it will be either an investigational new drug application (INDA) or a new drug application (NDA). If an INDA is approved and preliminary testing goes well, the maker should progress to an NDA. *See* 21 C.F.R. pts. 312, 314, 610 (2011) (specifying the process by which the FDA approves an application and the reasons that may justify rejection); CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES 4000.1–7800.1, *available at* http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm (last updated Nov. 21, 2012); *Investigational New Drug (IND) Application*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (last updated June 6, 2011) (noting the FDA requirement that there must be sufficient evidence from animal experimentation that the drug will not produce unreasonable safety risks to humans and can be developed into a marketable drug).

21. Getting the application to the right place is trickier than one might think. If most stem cell products are biologics or combination products in which the biological component dominates, applications for approval must, unless assigned elsewhere, go to the Center for Biologics Evaluation and Research (CBER). Any stem cell products classifiable as drugs are vetted by the Center for Drug Evaluation and Research (CDER). The picture is complicated by the fact that on October 1, 2003, the FDA shifted certain product oversight responsibility from CBER to CDER. Some biologics remain within CDER's purview. *See Therapeutic Biologic Applications (BLA)*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm (last updated Feb. 13, 2012) [hereinafter *CDER Products*] (listing cytokines, growth factors, enzymes, immunomodulators, thrombolytics, non vaccine immunotherapies, and certain proteins as under the CDER's review). The others, along with any stem cell drug products, go to the CBER. *See Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm (last updated May 12, 2010) [hereinafter *CDER Transfer*] (listing examples of products under each Center's supervision as a means of contrasting similar products that nonetheless are supervised by different Centers). Legislative authority for FDA jurisdiction resides in the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA), Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301–99). Regulatory details dwell in the Code of Federal Regulations. See 21 C.F.R. pts. 312, 314 for drugs. See 21 C.F.R. pts. 600, 610 for biological products.

22. Edison Pharm. Co. v. FDA, 600 F.2d 831, 836–37 (D.C. Cir. 1979).

which may not be easy for some stem cell products.[23]

A major complicating factor in this process for manufacturers of stem cell products is that manufacturers must slot their products into one of four existing legal pigeonholes: drug, device, biological product, or combination product.[24] The FDA is unlikely to put *all* stem cell products into any *one* of the four categories.

For example, few stem cell products are likely to be classified as a "drug" or a "device."[25] Physicians may use a device to *deliver* stem cell products to

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23. During the entire process, the maker must be forthright. The FDA has authority to impose strict recordkeeping requirements. *See* United States v. Garfinkel, 29 F.3d 451, 453, 455–57 (8th Cir. 1994) (deferring to the FDA's expansion of the recordkeeping requirement to cover clinical investigators as well as manufacturers). A maker can be indicted for withholding adverse information and results and for violating recordkeeping regulations. *See id.* at 453–54, 457–59 (responding to the claim that the FDA's authority to indict was unconstitutionally delegated by Congress). By law, the FDA must disclose safety and effectiveness data upon request, even in the case of abandoned applications. Controversially, in *Public Citizen Health Research Group v. FDA*, the D.C. Circuit held that this duty to disclose applied only to NDAs, not to INDAs. 185 F.3d 898, 902–07 (D.C. Cir. 1999) (interpreting 21 U.S.C. § 355(l)). The FDA may withdraw its approval if the stem cell product turns out, in light of new or suppressed evidence, to not be safe or effective. *See* 21 U.S.C. § 355(e) (2006) (giving these and other justifications for withdrawal); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 633 (1973) (holding that, despite § 355(e), an NDA remains effective unless it is suspended).

24. *See* 21 U.S.C. § 360bbb-2(a) (noting that the manufacturer can also determine the appropriate FDA authority under which to slot the product).

25. 21 U.S.C. § 321 states:

> The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Id. § 321(g)(1). Clauses (A), (B), (C), and (D) are broad enough that one or more of them might capture some stem cell products. In litigation, though, the FDA has at least once taken the position that stem cell products are both drugs and biological products. *See infra* text accompanying note 56 (remarking that the FDA found a manufacturer had improperly implanted cells without a license because a license was required for products classified as either drugs or biological products); *cf. infra* text accompanying note 61 (quoting a court decision to the effect that a particular stem cell product was both a "drug" and a "biological product" under federal legislation). However, due to the biological activity of such products, they are more likely to be seen as biologics. *See infra* note 27 (listing examples of products that fall under the category of biological products and noting that the FFDCA applies to such products). As to devices, § 321 provides:

> The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or

the right place in a patient's body, but the products themselves are not devices. Likewise, some cells derived from hESCs can generate drug-like proteins in large quantities—think of the immune interferon and other proteins produced by the cells from John Moore's body.[26] These proteins might be classified as drugs, but this category is generally not used for living cells or tissues that have continuing biological action, which includes most stem cell products.

Therefore, most stem cell products will likely be classified as "biological products," or "biologic" for short.[27] Stem cell products bear some comparison to both cellular and non-cellular biologics. Stem cell products are plainly analogous to cellular biologic products like whole blood and blood components because hematopoietic stem cells from umbilical cord blood qualify as blood components. Stem cell products are less analogous to non-cellular biologic products, such as vaccines and antitoxins, because stem cells can potentially be used to reconstitute or strengthen a patient's immune system or regenerate tissues and organs whereas most non-cellular biologics cannot.

Although stem cell products are broadly biologic in character, and some may fall exclusively into that category, many other stem cell products will probably fall into the category "combination product"—specifically, a combination of a biologic and a device. An FDA regulation defines a

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related article, including any component, part, or accessory, which is—

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Id. § 321(h).

26. *See* Moore v. Regents of the Univ. of Cal., 793 P.2d 479, 481 n.2 (Cal. 1990) (mentioning that scientists may be able to produce substantial numbers of proteins that have the potential for new treatments by isolating the gene responsible for generating such proteins).

27. 42 U.S.C. § 262(i) states that:

[T]he term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Id. With a minor exception, the FFDCA applies to biological products regulated here. *See id.* § 262(j) (stating the exception).

"combination product" as, in part, a "product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity."[28] Typical examples of combination products are glucose monitor/insulin pump systems, transdermal patches that allow drugs to enter the body slowly through the skin, and cardiac stents that disseminate an antibiotic into the surrounding site and the blood to reduce the risk of infection.[29]

Using stem cells and their derivatives therapeutically often requires delivery to an appropriate area of the body. Such delivery usually necessitates the use of a device. As a result, many stem cell products will likely be joined to a device to yield a combination product. For instance, some treatments for heart conditions might administer hematopoietic stem cells through catheters into the coronary arteries or into the myocardium, or inject cells through a needle during a coronary artery bypass graft. Another possible treatment might use a scaffold seeded with autologous stem cells for organ transplantation. This product would have the shape of the target organ and the autologous cells would allow the product to function, for example, like a natural human bladder. Such a product can in principle function without the usual problems of rejection.[30] Some combination products are already in development. Pfizer, Inc., for example, is developing an artificial membrane onto which ESC-derived eye cells are placed to treat macular degeneration.[31] These illustrations provide but a small window into possible combination products involving stem cell products.

The classification of a stem cell product by the FDA is important for two reasons. First, both application fees and pre-market review costs differ markedly depending on the classification. To illustrate, for the 2012 fiscal year the fee for a drug or biologic application requiring clinical data was

28. 21 C.F.R. § 3.2(e)(1) (2012). Other items falling under the heading of combination products include separate products that are packaged together or intended to be used together. *See id.* § 3.2(e)(2)–(4).

29. For these and other illustrations, see *Examples of Combination Product Approvals*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm (last updated July 15, 2010).

30. *See* Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49,848, 49,858 (Aug. 25, 2005) (to be codified at 21 C.F.R. pt. 3).

31. *See Stem Cells Demonstrated to Reverse Macular Degeneration Blindness,* BREAKTHROUGH DIGEST MED. NEWS (Apr. 19, 2009), http://www.breakthroughdigest.com/eye-ailments/stem-cells-demonstrated-to-reverse-macular-degeneration-blindness/ (reporting that ESC-derived eye cells placed on an artificial membrane and inserted in the back of the retina were successful in rats with a disease similar to age-related macular degeneration in humans).

approximately $1,841,500, whereas the standard pre-market application fee for a medical device was $220,050.[32] Predictably, manufacturers jockey to get their products classified to increase the chances of approval and hold down review costs.[33] Ultimately, higher total costs fall upon consumers, manufacturers, or both. These fees, imposed under the Prescription Drug User Fee Act (PDUFA),[34] may have enabled quicker review of new drugs, biologics, and devices.[35] Not only has the regulatory review time decreased,[36] but the number of approved new drugs, biologics, and devices has increased.[37]

It is possible to accelerate review further by using regulatory vouchers under the FDA Amendments Act of 2007.[38] These vouchers are transferable. So even though the voucher program was intended for drugs used to treat neglected diseases, a voucher holder could sell the voucher to

32. *See* Prescription Drug User Fee Rates for Fiscal Year 2012, 76 Fed. Reg. 45,831 (Aug. 1, 2011); Medical Device User Fee Rates for Fiscal Year 2012, 76 Fed. Reg. 45,826–27 (Aug. 1, 2011); *cf.* Mark Lavender, *Regulating Innovative Medicine: Fitting Square Pegs in Round Holes*, 2005 DUKE L. & TECH. REV. 0001, ¶ 8 (giving older figures).

33. For example, ultrasound contrast agents, which are combination products, are usually assigned to the CDER, but one manufacturer persuaded the Office of Combination Products (OCP) to assign its ultrasound contrast agent to the Center for Devices and Radiological Health (CDRH). *See* Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 29 (D.D.C. 1997) (holding that though the FDA has some discretion, it may not treat similar products differently without adequate justification). CDER and CBER standards for approval are generally more stringent than CDRH standards. Again, the difference in the full cost of pre-market review can be substantial. Two manufacturers whose products were reviewed in 1997 by the CDER had $1.5 million and $3.7 million more in expenses than would have been incurred under CDRH review. *Id.* at 29 n.9; Lavender, *supra* note 32, at ¶ 9.

34. 21 U.S.C. § 379(g)–379(h)(a) (Supp. II 2006).

35. The fact that user fees are contingent on the FDA's strict adherence to review timetables is probably at least partly responsible for this correlation (i.e. tying user fees to a specific, performance-based purpose or goal is directly related to improved application review times). *See* Susan Okie, *What Ails the FDA?*, 352 NEW ENG. J. MED. 1063, 1064 (2005); *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-02-958, FOOD AND DRUG ADMINISTRATION: EFFECT OF USER FEES ON DRUG APPROVAL TIMES, WITHDRAWALS, AND OTHER AGENCY ACTIVITIES 1, 3 (2002) [hereinafter GAO REPORT].

36. Okie, *supra* note 35, at 1064.

37. However, after the Prescription Drug User Fee Act's (PDUFA's) implementation, the following adverse consequences have been observed: shifting of FDA funds away from post-marketing safety surveillance; increased reviewer workloads; high reviewer turnover; reduced training for review teams; and inappropriate pressure to approve or recommend drug approval. *Id.* Moreover, a Government Accountability Office (GAO) report found that the rate of safety-related drug withdrawals significantly increased post-PDUFA. GAO REPORT, *supra* note 35, at 25–26.

38. 21 U.S.C. § 360n (Supp. II 2006).

a developer of stem cell products that target other diseases.[39] To some extent, manufacturers' quicker review times and patients' speedier access to new medicines and devices offset the higher review costs under the PDUFA. Whether the higher total costs are worth it to society depends on aggregative rather than product-specific judgments. For example, the aggregative judgment might be that the extra costs are regrettable because the products that get to market are more expensive than they otherwise would be. Alternatively, the aggregative judgment might be that the extra costs are worth bearing because they facilitate justifiably stringent regulation and monitoring.

Second, classification of a stem cell product as a biologic or combination product—or, perhaps, as a drug or device—has consequences within the internal bureaucracy of the FDA. The FDA has various centers that oversee the pre-market review and post-market regulation of these products.[40] Each center has its own staff, criteria, and culture, and each is largely self-governing.[41] Many innovative products possess features of two or even three classifications, and it is here that both detached legal observers and interested parties (such as manufacturers and FDA officials) must wrestle over which center should have primary jurisdiction.[42] Stem cell product manufacturers have a strong incentive to privilege monetary concerns over consumer safety in attempting to get a more favorable center for their products.[43]

Within the FDA, a product is classified as a combination product by the

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39. *Id* § 360n(b)(2). On the practical implications and the normative defensibility of the voucher program, see, for example, Aaron S. Kesselheim, *Drug Development for Neglected Diseases—The Trouble with FDA Review Vouchers,* 359 NEW ENG. J. MED. 1981 (2008), and Christopher-Paul Milne & Joyce Tait, *Evolution Along the Government-Governance Continuum: FDA's Orphan Products and Fast Track Programs as Exemplars of "What Works" for Innovation and Regulation,* 64 FOOD & DRUG L.J. 733 (2009). An unpublished work by my colleague Jon D. Michaels drew my attention to the voucher program.

40. For the jurisdiction of CDER and CBER, see *supra* note 21. The CDRH has jurisdiction over devices. FDA Product Jurisdiction, 21 C.F.R. §§ 3.2(b), 3.3–3.4 (2012). *See generally* Mary K. Olson, *Regulatory Agency Discretion Among Competing Industries: Inside the FDA*, 11 J.L. ECON. & ORG. 379 (1995). Criticism of CDRH for having a lower threshold for approval than CBER and CDER is severe. *See, e.g.*, INST. OF MED. OF THE NAT'L ACADS., MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS (2011), *available at* http://www.nap.edu/catalog.php?record_id=13150.

41. For an excellent peer-reviewed study of the criteria and processes across FDA centers, see Burgunda V. Sweet, Ann K. Schwemm, & Dawn M. Parsons, *Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products*, 17 J. MANAGED CARE PHARMACY 40 (2011), *available at* http://www.amcp.org/data/jmcp/40-50.pdf.

42. Lavender, *supra* note 32, at ¶¶ 1–4.

43. *Id*. at ¶¶ 10–11.

Office of Combination Products (OCP).[44] The assignment of a combination product turns on a judgment by the OCP as to the "primary mode of action," (PMOA) of the product.[45] Determining a product's primary mode of action can be quite complicated.[46]

Since stem cell products can be classified as biologics, combination products, or—less plausibly—drugs[47] or devices, the FDA's classification scheme, as applied to stem cell products, is especially susceptible to manipulation and classification problems. Manufacturers lobbying the FDA for a less costly classification of their product is, as detailed above, one manifestation of this problem.[48]

Other problems arise when the FDA must force a stem cell product into one of its pre-existing legal pigeonholes. For example, although most stem cell products can be plausibly classified as biologics, stem cell products encounter challenges that most noncellular biologics, such as toxins and antitoxins, do not. Most noncellular biologics are sterilizable and used within thirty days. In contrast, many stem cell products are likely to be cryopreserved for longer, which raises concerns about their stability and

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44. The OCP was created by the Medical Device User Fee And Modernization Act of 2002, Pub. L. No. 107-250, § 204, 116 Stat. 1588, 1611 (2002) (codified at 21 U.S.C. § 353(g) (2006)).

45. 21 U.S.C. § 353(g)(1) (2006). The term "primary mode of action" (PMOA) comes from the Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16(a), 104 Stat. 4511, 4526 (1990) (codified at 21 U.S.C. § 353(g)(1) (2006)).

46. Effective November 23, 2005, the FDA amended the final rule in 21 C.F.R. Part 3 to create a new definition and method for determining a combined product's PMOA. Definition of Primary Mode of Action of a Combination Product, 70 Fed. Reg. 49,848 (Aug. 25, 2005) [hereinafter PMOA Definition]. The PMOA is now defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." 21 C.F.R. § 3.2(m) (2011). Because the PMOA is often difficult to determine, the final rule has a two-tiered algorithm for determining the center to which the OCP should assign the combined product. The first tier explains that OCP should assign the combined product to the center that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. PMOA Definition, *supra*, at 49,850. If there is no similar combination product, then the combination product should be assigned to the center that has the most expertise related to the most significant safety and effectiveness questions presented by the proposed combined product. *Id.*

47. *But see infra* text accompanying note 56 (discussing the FDA's classification of certain mesenchymal stem cell mixes as both drugs and biologics).

48. One lawyer commented, "There's an incentive for sponsors of new products to be very strategic in how they portray their products to ensure primary review by one center or another." Hannah Waters, *Combination Products Neglected by FDA Device Evaluation*, 17 NATURE MED. 1024 (2011) (quoting Jason Sapsin, a former FDA attorney).

requires safeguards for the pre-freeze and post-thaw preservation of the products.[49] Additionally, many stem cell products—unlike most noncellular biologics—are unsterilizable, can support the growth of pathogens, and might be placed in sensitive sites such as the central nervous system.[50] There are also well-known technical difficulties with the sources of stem cells used in stem cell products. The FDA seems likely to pay special attention to these difficulties if the stem cell products come from iPSCs or stem cell nuclear transplants (SCNT).[51] Moreover, the FDA office that deals with cellular, tissue, and gene therapies should be alert to parallels between gene therapy and the therapeutic use of stem cell products: unsterilizability, uncertain purity, possible source of pathogens, and risks created by the ongoing biological activity of the new genetic material or cells.[52] In sum, the FDA classification system and its

49. *See, e.g.*, CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S FOOD & DRUG ADMIN., GUIDANCE FOR REVIEWERS: INSTRUCTIONS AND TEMPLATE FOR CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) REVIEWERS OF HUMAN SOMATIC CELL THERAPY INVESTIGATIONAL NEW DRUG APPLICATIONS INDS, 19–20 (Draft, Aug. 2003) [hereinafter SCT Draft Guidance], *available at* http://www.fda.gov/OHRMS/DOCKETS/98fr/03d0349gdl.pdf.

50. *See*, *e.g.*, Marcia Barinaga, *Fetal Neuron Grafts Pave the Way for Stem Cell Therapies*, 287 SCIENCE 1421 (2000); BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMM., BRMAC MEETING # 27: HUMAN STEM CELLS AS CELLULAR REPLACEMENT THERAPIES FOR NEUROLOGICAL DISORDERS 1 (Briefing Document for meeting on July 13–14, 2000, in Gaithersburg, Md.) (Draft, July 9, 2000) *available at* http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3629b1a.pdf.

51. As to iPSCs and iPS cells generally, "[C]loser scrutiny of their genetic integrity and differentiation behaviour has revealed subtle yet potentially significant differences from ES cells." George Q. Daley, *Imperfect Yet Striking*, 478 NATURE 40, 40 (2011). Daley continues:

> As well as provoking rogue genetic changes, reprogramming can leave vestiges of the original differentiated (somatic) cell's identity—known as epigenetic memory—through faulty remodelling of chemical modifications on DNA and its associated proteins.

Id. In regard to stem cell nuclear transplants (SCNTs), the usual process has been to remove the genome (the haploid nucleus) from a human oocyte and replace it with the diploid nucleus of a fully differentiated adult cell such as a skin fibroblast. But it has proved hard to develop ESC lines from this maneuver, for growth arrest tends to occur at the six- to ten-cell stage. A recent study describes the insertion of the fibroblast in an oocyte that still has its haploid nucleus. This technique allows a blastocyst containing some 70 to 100 cells to develop. However, these are triploid cells and hence genetically anomalous. *Id.*; Scott Noggle et al., *Human Oocytes Reprogram Somatic Cells to a Pluripotent State*, 478 NATURE 70, 74–75 (2011).

52. *See, e.g.*, SCT Draft Guidance, *supra* note 49, at 1, 13–18; CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GENE THERAPY CLINICAL TRIALS—OBSERVING SUBJECTS FOR DELAYED ADVERSE EVENTS (Recommendations, Nov. 2006), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Cellular

accompanying bureaucratic centers will play a key role in scrutinizing stem cell products and evaluating the risks associated with them.[53]

Although the FDA has asserted jurisdiction over stem cell products, and what some authors call stem cell treatments, for two decades,[54] the matter is in litigation pending an appeal. Regenerative Sciences, LLC (Regenerative Sciences), is a Colorado firm that isolates mesenchymal stem cells (MSCs) from bone marrow. It then cultures the cells, adds some materials, and uses the mix for injection into patients. Its main treatment is called "Regenexx-C"; the "C" stands for "Cultured."[55] In 2008, the FDA sent a warning "letter to Regenerative Sciences stating that, based on the way the use of MSCs was being promoted on the Regenexx website, it considered those cells to be drugs and biological products" over which the FDA had authority.[56] The company's position was that its MSCs were not drugs or

andGeneTherapy/ucm078719.pdf. FDA action is particularly evident in the case of somatic cell therapy for cardiac diseases, and this therapy would include stem cells. *See* U.S. FOOD & DRUG ADMIN. GUIDANCE FOR INDUSTRY: SOMATIC CELL THERAPY FOR CARDIAC DISEASE (2010), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM164345.pdf; *see also* Draft Guidance for Industry: Somatic Cell Therapy for Cardiac Disease; Availability, 74 Fed. Reg. 14,992 (Apr. 2, 2009).

53. It is doubtful that the Biologics Price Competition and Innovation Act of 2009 (Biosimilars Act), Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010) (to be codified at 42 U.S.C. § 201), will have any short-term impact on stem cell products. There are few such products on the market, and the test for biosimilarity will be hard to satisfy for these products. CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT (Draft Guidance, Feb. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM291128.pdf.

54. Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248–51 (Oct. 14, 1993).; *see also* United States v. Loran Med. Sys., Inc., 25 F. Supp. 2d 1082, 1084 (C.D. Cal. 1997) (issuing a permanent injunction on the importation of neonatal cells); CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GUIDANCE FOR HUMAN SOMATIC CELL THERAPY AND GENE THERAPY 3 (1998), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm081670.pdf; Donald W. Fink, *FDA Regulation of Stem Cell-Based Products*, 324 SCIENCE 1662 (2009). For use of the term "stem cell treatments," see RUSSELL KOROBKIN, STEM CELL CENTURY: LAW AND POLICY FOR A BREAKTHROUGH TECHNOLOGY 232–57 (2007). Korobkin believes that the FDA has "the authority to require premarket approval of stem cell treatments," but adds that "[w]hether and when the FDA should exercise this statutory authority . . . is a different question." *Id.* at 243.

55. *Regenexx Procedures Family—Stem Cell and Platelet Procedures,* REGENEXX, http://www.regenexx.com/regenexx-procedures-family/ (last visited Nov. 9, 2012).

56. Barbara von Tigerstrom, *The Food and Drug Administration, Regenerative Sciences, and the*

biologics and that the FDA was interfering with the practice of medicine. Eventually, the company sued the FDA for injunctive and declaratory relief. A federal district court granted the FDA's motion to dismiss on ripeness grounds because the FDA had not yet attempted to regulate Regenerative Sciences.[57] In June 2010, Regenerative Sciences "applied for an order 'to prompt FDA to take "final agency action" or leave its medical practice alone.'"[58] Later, the FDA sought an injunction and ultimately, in January 2011, moved for summary judgment and dismissal of the defendants' counterclaims.[59]

In the newly captioned *United States v. Regenerative Sciences, LLC*,[60] the court ruled in favor of the United States and granted its request for a permanent injunction against the defendants. The court said that "the cell product used in the Regennex Procedure meets the statutory definition for both a 'drug' under the FFDCA and a 'biological product' under the PHSA."[61] The court then concluded that Regenerative Sciences' cultured mesenchymal stem cell products amount to a "drug" under federal law.[62] One might cavil whether Regenerative Sciences' MSCs are better classified as a biological product or as both a drug and a biological product. In any event, the thrust of the decision is sound because of the amount of manipulation the MSCs received and because of the need to control inadequately vetted stem cell products.

This case is interesting partly because of its political valence. The protests of Regenerative Sciences prior to the injunction had become a rallying cry against FDA regulation. Two articles addressed this litigation while it was in progress. One acknowledged that Regenerative Sciences was likely to lose but contended that "the FDA should recognize that it makes little sense to impose a regulatory framework developed for mass manufacturers on small physician practices."[63] The majority shareholders

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Regulation of Autologous Stem Cell Therapies, 66 FOOD & DRUG L.J. 479, 482 (2011).

57. Regenerative Sciences, Inc. v. FDA, No. 09-CV-00411-WYD-BNB, 2010 WL 1258010, at *7 (D. Colo. Mar. 26, 2010). The company sometimes drops "LLC" and calls itself Regenerative Sciences, Inc.

58. von Tigerstrom, *supra* note 56, at 483.

59. *Id.*

60. United States v. Regenerative Sciences, LLC, No. 10-1327, 2012 WL 2989988 (D.D.C. July 23, 2012).

61. *Id.* at *8.

62. Jocelyn Kaiser, *U.S. Federal Court Says Stem Cell Treatments Are Drugs,* SCIENCE INSIDER, (July 26, 2012, 2:46 PM), http://news.sciencemag.org/scienceinsider/2012/07/us-federal-court-says-stem-cell-.html?ref=hp.

63. Mary Ann Chirba & Stephanie M. Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?,* 7 J. HEALTH & BIOMEDICAL L. 233, 272 (2011). There is a good deal of space

of Regenerative Sciences are two physicians who operate a clinic in Broomfield, Colorado, where, prior to the injunction, they injected Regenexx-C into patients.[64] But the crucial point is not the size of the laboratory or manufacturer. What is crucial is the nature and degree of the manipulation of the components of Regenexx-C. To create this product, MSCs are harvested from the patient's hip. The patient's blood is then drawn to isolate growth factors. Finally, using the MSCs, growth factors, reagents, and culture media, Regenerative Sciences increases the number of MSCs that go into Regenexx-C.[65] The manipulation of these ingredients is sufficiently intensive to warrant FDA oversight. This is not a case of regulation run wild.

Barbara von Tigerstrom, a well-known writer on stem cell technology and tissue engineering, was the author of the other article on this litigation while it was in progress. She makes a strong case that the FDA's regulation in this situation is "eminently reasonable."[66] It would be even more reasonable in cases involving allogeneic, rather than autologous, stem cell products and treatments, and in cases using autologous human induced pluripotent stem cells (hiPSCs).[67] Regulation is also needed to thwart stem cell tourism, whether within or outside the United States, because insufficiently vetted stem cell products pose health risks no matter where the products are administered.[68]

III. STEM CELL PRODUCTS AND THE REVISION OF ADMINISTRATIVE LAW

As we move to the prospect of revising current administrative law, it is important to have a more general understanding of when regulation, and of what sort, is justifiable. I immediately put one possible view to the side: that there ought not to be any administrative regulation of, or indeed any other form of governmental control over, stem cell products. Such a

between the dichotomous terms in the title of their article.

64. The physicians have ceased doing so until the lawsuit is finally decided. However, von Tigerstrom, *supra* note 56, at 481–82, reports that the company "has licensed its technology to clinics offering it in China and Argentina, and is opening a stem cell culture lab in the Cayman Islands." Stem cell tourism, anyone?

65. *See* von Tigerstrom, *supra* note 56, at 480.

66. *Id.* at 506. For a brief commentary on the case, see Tamra Lysaght & Alastair V. Campbell, *Regulating Autologous Adult Stem Cells: The FDA Steps Up*, 9 CELL STEM CELL 393 (2011).

67. Paul S. Knoepfler, *Key Anticipated Regulatory Issues for Clinical Use of Human Induced Pluripotent Stem Cells*, 7 REGENERATIVE MED. 713 (2012).

68. Alex Philippidis, *Stem Cell Tourism Hardly a Vacation,* GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Aug. 16, 2012, http://www.genengnews.com/insight-and-intelligenceand153/stem-cell-tourism-hardly-a-vacation/77899669.

position would just rely on the market to sort out ways of responding to these products. I reject this view because there is, especially in such a new and unpredictable area as stem cell products, little justification for leaving all governance in this area to willing buyers and willing sellers. It is far too difficult for everyone to obtain and process all of the relevant information. Further, at this time, stem cell products do not satisfy the ideal market dynamic of perfect competition, for there are few producers or sellers that are willing and able to supply stem cell products and there are high barriers to entry.

Thus, to me, it is a nonstarter to argue that there ought to be no regulation at all in the area of prescription drugs, medical devices, and stem cell products. Given that, the question then becomes what shape regulation ought to take.[69]

Compared to an utter lack of regulation or obviously irrational regulation, the current administrative scheme for FDA regulation of stem cell products might seem broadly sensible. But can it be better? I discuss this question under two headings: sui generis regulation and a proposal offered by Dina Gould Halme and David A. Kessler.[70] I then offer, in Part IV, a new regulatory proposal that differs from, and is superior to, both of these.

A. Sui Generis Regulation

Some scholars believe that the FDA ought to regulate less than, and differently from, the way that it currently does.[71] Because stem cell

69. Unlike administrative agencies in some European countries, the FDA does not regulate prices. However, Congress has made generic drugs more readily available once the patent on a branded drug has expired, which tends to make the same compound available at a lower price. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (known as the Hatch–Waxman Act), (codified as amended at 15 U.S.C. §§ 68b–68c; 21 U.S.C. §§ 301, 355, 360cc; 28 U.S.C. § 2201; 35 U.S.C. §§ 156, 171, 282 (2006)); Mary K. Olson, *Pharmaceutical Regulation, in* 3 THE NEW PALGRAVE DICTIONARY OF ECONOMICS AND THE LAW 40, 41, 44–45 (Peter Newman ed., 1998).

70. The FDA has already issued a "draft guidance" for Risk Evaluation and Mitigation Strategies (REMS). CTR. FOR DRUG EVALUATION & RESEARCH & CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION & MITIGATION STRATEGIES (REMS), REMS ASSESSMENTS, AND PROPOSED REMS MODIFICATIONS (2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

71. If MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (2004), is overly critical of the pharmaceutical industry, RICHARD A. EPSTEIN, OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION (2006), is too uncritical of it and unduly chastises

products will be new, it could be argued that they should have their own center in the FDA and that special regulations should apply to them. John Miller constructs an analogous argument for nanomedicine—various drugs, diagnostics, devices, and delivery systems that make use of extraordinarily small molecular structures.[72]

But stem cell products and regenerative medicine are not wholly analogous to nanomedicine. Although the eventual products of nanomedicine are unknown, they fall into all of the FDA's existing categories. In contrast, stem cell products will be mainly biologics, even if many of the products will require a delivery device. Moreover, while no FDA center has substantial expertise in the full range of nanomedical inventions, the FDA center that deals with biologics already has expertise in inventions related to stem cell products, such as vaccines, blood products, and gene therapies. It would be foolish to waste this expertise by creating a new FDA center having exclusive jurisdiction over stem cell products.

But in one critical respect stem cell products and nanomedicine are at least partly analogous. Both deal with innovative products that have the potential for enormous benefits and grave harms. That is why I am able, in Part VI.B.1, to project features of my integrated regulatory–product liability proposal onto nanotechnology generally (not just nanomedicine). The implications of my integrated proposal for nanomedicine differ in three ways from Miller's view. First, a special FDA center for nanomedicine is unnecessary. Second, nanomedical products should be regulated more stringently than he suggests. Third, his nanomedical proposal lacks the generalizability that my integrated proposal for stem cell products possesses.

In any event, promulgating sui generis regulations for stem cell products would needlessly make the law more complicated. No final judgment should be made on special regulations for these products without examining a detailed regulatory proposal. The issues and risks posed by many foreseeable stem cell products are akin to those posed by cellular and

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the FDA. For any article on stem cell products, the chief limitation of Epstein's book is its concentration on drugs at the expense of biologics and medical devices. Evenhanded reviews of his book are scarce. Despite the book's clarity and forcefulness, in my judgment it undervalues the usefulness of clinical trials, indulges in neoclassical economic argument over empirical data, mis-assimilates drugs to the general run of commercial products, and fails to explore adequately the merits of some government intervention such as the use of public oversight and (very rarely) march-in rights. *Cf.* MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY 212–42 (2008) (analyzing the pharmaceutical industry); Arnold S. Relman, *To Lose Trust, Every Day*, THE NEW REPUBLIC, July 23, 2007, at 36 (providing useful, if not always balanced, criticisms of Epstein's book).

72. John Miller, Note, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. 2, 5 (2003).

gene therapies, as well as vaccines.[73] An evenhanded account is needed of the similarities and differences between existing biologics and predicted stem cell biologics.

A tension would exist if (1) sui generis regulation of stem cell products were rejected and (2) exactly the same differences and similarities existed between stem cell products and other, more familiar biological products. However, there are similarities between stem cell products and traditional biologics in some respects and differences in other respects. Thus proposition (2) is false, which rules out any objectionable tension. If my account of the close connections between predicted stem cell products and existing biologics is sound, then skepticism about sui generis regulation is warranted.

Some have suggested that because stem cell products return human-derived items to the body they should be regulated *less* stringently than would apparently be the case under current FDA regulations. In my opinion, if the products consist of stem cells that are from the patient's own body, they could be regulated less stringently, unless they have been significantly manipulated.

But if the products involve stem cells from someone other than the patient, then I doubt the soundness of less stringent regulation for two reasons. First, most stem cell products will probably be classified as biologics or as combination products in which the biologic component is primary. Given the risks associated with biologics, FDA regulation ought not to be eased.[74]

Second, most stem cell derived therapies will probably be cellular rather than noncellular biologics. Unlike noncellular biologics, such as viruses, vaccines, toxins, and antitoxins, cellular biologics are unsterilizable. Further, stem cell derived cellular biologics can come, so far as is currently

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73. For example, just as one of the potential adverse events associated with gene therapy includes treatment-induced cancers, there are questions about the transformation of hESCs, iPS cells, and their derivatives into cancerous tumor cells. *E.g.*, Salima Hacein-Bey-Abina et al., *Insertional Oncogenesis in 4 Patients After Retrovirus-Mediated Gene Therapy of SCID-X1*, 118 J. CLINICAL INVESTIGATION 3132 (2008); Chu-Chih Shih et al., *Issues in Development: Human Embryonic Stem Cells Are Prone to Generate Primitive, Undifferentiated Tumors in Engrafted Human Fetal Tissues in Severe Combined Immunodeficient Mice*, 16 STEM CELLS & DEV. 893 (2007).

74. There should be an exception in the case of stem cell therapies in human clinical trials that qualify for Orphan Drug and Fast Track status. *See, e.g.*, *FDA Fast-Track Clearance Expedites Stem Cell Therapy*, OSIRIS THERAPEUTICS, INC., http://www.osiristx.com/clinical.php (last visited Nov. 30, 2012) (discussing Prochymal, a formulation of mesenchymal stem cells intended for intravenous administration to treat acute and steroid-refractory GVHD and Crohn's disease, which was then in Phase III clinical trials). Osiris's Prochymal has been approved by Canadian regulators but not yet by the FDA. *See supra* note 2.

known, from only two sources. One source is individuals other than the patient. Since the biologics in question will have the DNA of someone other than the patient, the match might be imperfect. Even in the special case where the cell donor is the patient's identical twin, the DNA of monozygotic twins tends to differ a bit over the years because of transcriptional errors and random mutations. The donor's cells may also harbor viruses or antibodies that could prove harmful to the patient. A different source of stem cell derived cellular biologics is via SCNT. The *nucleus* of the cells would have the patient's DNA. But the *mitochondria*—organelles within the cell but outside the nucleus—would come from the egg donor and have different DNA from the mitochondrial DNA of other somatic cells in the patient's body. The risks associated with different mitochondrial DNA are not well understood at present but cannot be assumed to be zero.[75]

Stem cell products are likely to be similar enough to existing biologics to permit an effective regulatory scheme to build on already applicable sensible protocols. Still, because of the special nature of most stem cell products, they offer risks that merit maintaining the same degree of vigilance with which the FDA has dealt with existing biologics. Thus, sui generis regulation as a first step is unnecessary and ill-advised.[76]

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75. I leave to one side the rare case in which the egg donor and the patient are the same person. The FDA has asserted jurisdiction over and sought INDAs for work on ooplasm transfer, which is involved in almost all techniques of SCNT. Lawrence B. Ebert, *Lessons to Be Learned from the Hwang Matter: Analyzing Innovation the Right Way*, 88 J. PAT. & TRADEMARK OFF. SOC'Y 239, 254 (2006); Margaret Foster Riley & Richard A. Merrill, *Regulating Reproductive Genetics: A Review of American Bioethics Commissions and Comparison to the British Human Fertilisation and Embryology Authority*, 6 COLUM. SCI. & TECH. L. REV. 1, 5 nn.16–18 (2005); *see also* Jonathan R. Friedman et al., *ER Tubules Mark Sites of Mitochondrial Division,* 334 SCIENCE 358, 358–62 (2011) (illuminating the way in which mitochondria divide in cell mitosis); Justin C. St. John et al., *The Potential Risks of Abnormal Transmission of mtDNA through Assisted Reproductive Technologies*, 8 REPROD. BIOMEDICINE ONLINE 34 (2003) (explaining some risks involving mitochondrial DNA); *supra* note 74.

76. FDA's current treatment of stem cell products reinforces this conclusion. CBER and CDRH consider these products to be a subclass of HCT/Ps, or human cells, tissues and cellular and tissue-based products. Some HCT/Ps have nothing to do with stem cells. An example is Gintuit, "a cell-based treatment for gum recession developed by . . . [o]rganogenesis." Charles Schmidt, *Gintuit Cell Therapy Approval Signals Shift at U.S. Regulator,* 30 NATURE BIOTECHNOLOGY 479 (2012). The only stem cell products approved by the FDA at this time are Hemacord and HPC, cord blood. *See supra* note 2. *See generally* E-mail from Paul Richards, Public Affairs Specialist for CBER, to Douglas Wolfe, research assistant to the author (June 11, 2012, 2:11 PM) (on file with the author) (explaining FDA classification of stem cell products).

B. The Halme and Kessler Proposal

In 2007, Halme and Kessler floated an admirably terse proposal for FDA regulation of therapies based on stem cells,[77] which also addresses "stem cell products" as understood here. Halme and Kessler approach this matter from the perspective of medical researchers. They suggest a framework for categorizing four risks associated with stem cell therapies and products.[78] The risks are: possible transmission of genetic or infectious diseases; possible contamination or damage caused by cell processing; possible adverse effects of different cell mixes and different levels of purity, potency, or both; and possible adverse events *in vivo*.[79] Later, Halme and Kessler reorganize the risks into a chart that segregates cell type, purity, and potency. They evidently contemplate that their proposal should have some impact on FDA regulation.

Halme and Kessler's treatment of this matter has many advantages. It is thoughtful and methodical. Their article, appearing as it does in a major medical journal, identifies risks that matter greatly to its readership, especially medical researchers and specialist physicians. It also differentiates among risks in a way that is likely to aid policy analysts in the FDA. It recognizes that the current regulatory model for biologics is likely to be appropriate for stem cells.[80] Up to this point, I would happily incorporate these advantages into my more ambitious proposal.[81]

Nevertheless, Halme and Kessler's treatment also has some disadvantages. It is not very probing in regard to how the different identified risks might overlap, or even interact, with each other. Some risks identified in their discussion could affect more than one category in their chart. For example, disease contamination could adversely affect both purity and potency. Furthermore, their treatment only indirectly aids firms that are trying to decide whether to pursue lines of stem cell research and development, when to submit a stem cell product to the FDA for approval, or how to slot their application into the existing centers of the FDA. Such firms will need to work backwards from the terms of Halme and Kessler's proposal and what they already know about the FDA and its procedures to make decisions. Finally, non-specialist physicians and the educated general population might not find Halme and Kessler's categories very easy to use in making decisions. They might not be able to figure out whether tissue

77. Dina Gould Halme & David A. Kessler, *FDA Regulation of Stem-Cell-Based Therapies*, 355 NEW ENG. J. MED. 1730 (2006).

78. *Id.* at 1731–34.

79. *Id.*

80. *Id.* at 1735. They do not address combination products. *See generally id.*

81. *See supra* notes 77–80; *infra* notes 86, 117.

contaminated during processing is more dangerous to a particular patient than an unpredictable mix of pluripotent and multipotent cells, or than the possible migration of these cells from the implantation site.[82]

IV. A NEW REGULATORY PROPOSAL

This Article, I submit, has two primary virtues. One is a sensitive, on-the-ground touch for the inner workings of the FDA and the decisions manufacturers must make in the research and development of stem cell products. Such a concern for the realities of stem cell production is necessary to craft a regulatory scheme that ensures consumer safety without retarding innovation of new products.[83] The other primary virtue of this Article is that it shows how my regulatory proposal, detailed below, and my product liability proposal, which I have put forward elsewhere,[84] interlock and shed light on the integration of administrative law and product liability law more generally.

The following proposal offers recommendations for pre-market approval of stem cell products, post-market regulation of these products, and a risk-management and risk-reduction system. Together, these suggestions favor giving the FDA a more robust role than it currently has. As indicated earlier, I incorporate the advantages of the Halme and Kessler proposal.[85] Chief among these advantages is the presentation of the risks of stem cell products in terms of cell type, purity, and potency.[86]

Four factors circumscribe my proposal. First, if the level and degree of regulation of a particular stem cell product should be proportionate to the risk it poses, it is crucial to acknowledge that there is currently little reliable information about risks associated with stem cell products. The lack of information presents a challenge both to administrative regulation and to the operation of the market in this area. Further, a "meta" regulatory issue arises. Since the FDA would have a role in determining the degree of risk, it would also have a role in determining the degree of its regulatory power. The meta-issue is whether it is wise for the FDA to have this power.

Second, because my proposal suggests that the FDA should play a more aggressive role, at some point my proposal must be lodged within a general project of assessing the FDA and, if necessary, reforming it. For instance,

82. It would be churlish to fault Halme and Kessler for not solving problems that were absent from their agenda or for not reaching audiences that the *New England Journal of Medicine* regards as outside its scope.

83. The best recent study of the FDA is DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010).

84. Munzer, *supra* note 1.

85. *See supra* text accompanying note 81.

86. Halme & Kessler, *supra* note 77, at 1732–33.

discussions about raising application fees to support hiring more FDA personnel to process stem cell product applications inevitably feed into larger questions about tying application fees to strict timelines for decisions on applications. Again, conversations about a greater FDA role in post-market surveillance of stem cell products ineluctably involve larger questions about the FDA's authority to monitor all drugs, devices, and biologics once they have entered the market. These issues, though critically important in their own right, fall outside the scope of this Article.

Third, my proposal attempts to account for the various ways in which more regulation can backfire. Obviously, regulation comes with various costs, such as increases in the price of stem cell products and time to market. To be effective, regulation must produce benefits that outweigh its extra costs. Less obviously, making regulation transparent can sometimes introduce perverse incentives. Daniel Cahoy refers to this phenomenon as the "transparency paradox."[87] In fact, it is not a paradox but a predictable result of rejiggering the rules of tort and administrative law. Yet the phenomenon is important, and my proposal takes pains to avoid it.[88]

Fourth, the regulatory reform proposed here depends in part on the product liability analysis to be summarized in Part VI. As mentioned at the very beginning of this Article, any revamping of administrative law should take into account the justifications for altering the product liability regime. The regulatory reforms suggested here interlock with the proposal for reforming product liability law.[89] Thus, the achieved integration helps to make my proposal generalizable to other areas at the intersection of tort and administrative law.

A. The Core of the Proposal

Because so much uncertainty surrounds the risks associated with stem cell products, the FDA should play a more aggressive role than usual in deciding which of these products should be allowed on the market and what instructions, warnings, and restrictions on use should be applied. To illustrate the unknown risks of stem cells, consider the case of a patient with lupus nephritis, a disease in which the immune system attacks the kidneys. Her physicians injected her own hematopoietic stem cells directly into her

87. Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623 (2007). With respect, I prefer to reserve the word "paradox" for logical, semantic, and epistemic paradoxes, of which Russell's paradox, Grelling's paradox, and the examination paradox are respective examples. For a lucid exposition of these paradoxes, see R.M. SAINSBURY, PARADOXES 107–14, 123–27, 142–45, 162 (3d ed. 2009).

88. *See infra* text accompanying notes 107–16; Munzer, *supra* note 1.

89. *See infra* Part VI.A.

kidneys. Six months later she developed cellular masses in her kidneys, adrenal glands, and liver, which researchers believed to be stem cell derived or induced.[90] Although causation has not been established, this case is a warning flag for unknown risks and the uncertainty of side effects.[91]

The FDA must concentrate above all on safety risks and risks of ineffectiveness. So far as safety risks are concerned, the FDA should refuse to allow the marketing of any stem cell products whose risks are deemed unacceptable for virtually all patients. It might, though, permit the nonmarket employment of such products under its compassionate-use program.[92] Even if the risks of a given product are acceptable, the FDA, in its discretion, may ask for additional safety information so that patients and physicians can make informed decisions. Once a product has been approved for sale and has gone on the market, the FDA should require manufacturers and physicians to keep it abreast of changes in risks to safety. The risks might rise, decline, or differ from what they were at the time of approval. The FDA should disseminate this information promptly in the clearest form possible.

As to the effectiveness of stem cell products, plainly the FDA should not allow utterly ineffective products to go on the market at all. Marginally effective products ought to be allowed only if no other treatments are available and the products pose little in the way of safety risks. As with safety, the FDA should monitor the effectiveness of products on the market. It should ask manufacturers and physicians to keep track of departures, up or down, from the effectiveness profile at the time of approval for marketing. It should update all concerned parties of changes in the effectiveness of these products as promptly and as clearly as possible.

In connection with both safety and effectiveness, the FDA should implement a systematic program for risk management and risk reduction. If it deems a risk unacceptable, it should explain its reasoning so that patients and physicians understand the reasons for the product's unavailability. The best way to achieve this goal is to give patients and physicians access to risk-evaluation information through a transparent process. Doing so will also give designers and manufacturers of stem cell products an opportunity to improve the safety and effectiveness profiles of their products.

The FDA should have similar provisions for products with acceptable

90. Duangpen Thirabanjasak et al., *Angiomyeloproliferative Lesions Following Autologous Stem Cell Therapy*, 21 J. AM. SOC'Y NEPHROLOGY 1218 (2010).

91. David Cyranoski, *Strange Lesions After Stem-Cell Therapy*, 465 NATURE 997 (2010); Andras Nagy & Susan E. Quaggin, *Stem Cell Therapy for the Kidney: A Cautionary Tale*, 21 J. AM. SOC'Y NEPHROLOGY 1070 (2010).

92. 21 C.F.R. § 312.300, 312.305 (2012).

levels of risk. Here, though, the FDA must recognize that many decisions have to be made by patients and physicians on an individual basis. For example, a grave risk may be justified in the case of a patient with an apparently terminal illness, because the benefit of a cure or even a marginally effective treatment may be enormous. Although it is certainly worth the FDA's time to catalog minor risks, it should focus mainly on serious and unpredictable risks. Moreover, the FDA should institute a program for risk reduction. Granted, most efforts to lower risk ought to come from the designers and manufacturers of stem cell products. Yet, the FDA's familiarity with different classes of such products should enable it to tell designers, manufacturers, and physicians how to reduce these risks.

Institutionally, CBER is the best place for the FDA to deal with risk. The arguments for a separate center for stem cell products are wanting, at least given current information.[93] CBER has more relevant expertise than any other FDA Center. For combination products using stem cells, cooperation between the OCP and CBER is essential. Within CBER, those departments that deal with noncellular biologics, such as toxins and antitoxins, are less likely to have relevant expertise than those that deal with infracellular biologics such as viruses and gene therapy and cellular biologics such as vaccines and blood products.

Nevertheless, since there are still difficulties with trying to assimilate vaccines to stem cell products, the FDA should establish a new department within CBER to assess the safety and effectiveness of stem cell products, which it can do by reassigning existing personnel as desired and hiring new scientists as necessary.[94] Here, the FDA can look to tort litigation regarding biologic–device combination products, gene therapies, and blood products to get some idea of the expertise required. Moreover, within the last two decades universities have trained many new scientists with experience in stem cell biology. Some of these individuals can bring much needed knowledge to the FDA enterprise of evaluating stem cell products submitted for approval by manufacturers.

As to combination products, it appears that currently the OCP would assign stem cell combination products based on the product's PMOA. However, such products could instead be assigned to the new stem cell department in CBER with a recommendation that the OCP seek aid from other FDA centers based on their relevant expertise. The chief advantages of this alternative include (1) reducing the time, effort, and money spent by manufacturers in jockeying to get review by what they consider a more favorable center and (2) promoting consistency within the FDA's internal

93. *See supra* Part III.A.
94. *See supra* Part III.A.

bureaucracy about the approval and monitoring of stem cell combination products.

The Critical Path Initiative (CPI) sheds further light on the FDA's role in evaluating and promoting stem cell products.[95] Even now CBER receives funding to "[f]acilitate development of treatments using neural stem cells to replace degenerative brain cells."[96] It also gets funds to "[d]etermine whether it is possible to track neural stem cells after transplantation using magnetic resonance imaging (MRI)."[97] This second project aims to ensure the safety and effectiveness of using such stem cells before they are allowed on the market. To this end, it will try to evaluate a possible biomarker for tracking neural stem cells once scientists transplant them into the brains of mice. If the project pays off, it will shed light on the engraftment, differentiation, and fate of these stem cells. The CPI does not have enough money to make CBER an independent player in the market for stem cell products, but it does support programs that add to CBER's expertise and its capacity to assess safety and effectiveness.

B. Strengthening Pre-Approval Requirements and Pre-Clinical Administrative Review

The best antidotes for inadequate information are more and better information. In light of concerns about the lack of understanding of the basic biology of stem cells,[98] the FDA and the federal government would do well to revisit their experience in addressing heart disease, stroke, and HIV infection. In these cases, "[D]iscoveries in basic science were made through government-funded research, but effective drugs were developed in the private sector."[99] Discoveries made by bench scientists will provide both more information and, because of the peer review process, arguably better information. Research and development in the private sector are likely to yield both more and better information. This information might be more practically oriented than that produced by academic bench scientists.

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95. U.S FOOD & DRUG ADMIN., THE CRITICAL PATH INITIATIVE: PROJECTS RECEIVING CRITICAL PATH SUPPORT FISCAL YEAR 2008 13–14 (April 2009), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM186110.pdf.

96. *Id.* at 11. This source does not explicitly state that CBER receives any of its funding from the Critical Path Initiative (CPI).

97. *Id.* at 12. Both projects involve murine stem cells and collaboration between the FDA and the National Institutes of Health (NIH) Mouse Imaging Facility. *Id.* at 11–14.

98. Yan Leychkis, Stephen R. Munzer & Jessica L. Richardson, *What Is Stemness?,* 40 STUD. HIST. & PHIL. BIOLOGY & BIOMEDICAL SCI. 312 (2009); James M. Wilson, *A History Lesson for Stem Cells,* 324 SCIENCE 727 (2009).

99. Alastair J. J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618, 618 (2006).

Based on better information and understanding, the FDA should consider strengthening its pre-approval requirements and pre-clinical regulatory review.[100] As a general matter, and at least while stem cell products are in early stages of development, the FDA should be cautious in allowing accelerated or fast-track review of applications for these products. Instead, the FDA should ask manufacturers to improve their pre-approval clinical trials to ensure the safety of stem cell products. For example, the FDA can demand longer-term clinical trials, reduced reliance on surrogate outcomes, and higher numbers of trial participants who are more representative of the target population for the product.[101] It must, though, take into account the costs to manufacturers and consumers in making these changes to ensure that increased safety justifies the expenditures.

The FDA would do well to develop relevant standards for testing and approving stem cell products. These standards generally reside in "guidance" and "best practices" documents. Documents of this sort would not only aid reviewers in a thorough and objective review of applications, they would also help manufacturers and researchers to develop their products with a keen eye on safety and effectiveness, thereby helping them to submit successful applications. To illustrate, the FDA could issue guidelines for the processing, storage, and distribution of stem cell products, and for the most sensible pre-clinical and clinical trial protocols. In issuing such guidelines, the FDA might build on the principles enunciated by the International Society for Stem Cell Research.[102] As a different illustration, the FDA could take a page from its own experience with human gene therapy, where it published a guide to assist reviewers in evaluating INDAs.[103] The content of such a guide for stem cell products would have

100. *Cf.* Wilson, *supra* note 98, at 727–28 (expressing concern about the safety and usefulness of introducing hESCs and iPS cells in patients in regard to engraftment, rejection, toxicity, and tumorgenicity).

101. Warrant for these changes lies in relevantly similar experience with drug approvals. Clinical trial results submitted with an NDA or INDA rarely "provide comprehensive information on possible adverse events." U.S. GOV'T. ACCOUNTABILITY OFFICE, GAO-00-21, ADVERSE DRUG EVENTS: THE MAGNITUDE OF HEALTH RISK IS UNCERTAIN BECAUSE OF LIMITED INCIDENCE DATA 9 (2000) (pointing out that the number of patients in pre-approval clinical trials is usually too small to detect less-frequent adverse results, and that patients in such trials are imperfectly indicative of the full range of consumers who will use the drug (because trial participants are usually not elderly, seriously ill, and taking many other medications)).

102. INT'L SOC'Y FOR STEM CELL RES., GUIDELINES FOR THE CLINICAL TRANSLATION OF STEM CELLS (2008), *available at* http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf.

103. CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR FDA REVIEWERS AND SPONSORS: CONTENT AND REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) INFORMATION FOR HUMAN GENE THERAPY

to be rather different, for gene therapies are infracellular, but once again CBER would be the most appropriate FDA center to take the lead in developing the suggested guidance.

These suggestions reveal more potent advantages than disadvantages. True, there is some chance of increased costs and time delay. All the same, these suggestions have the advantage of improving the safety and effectiveness of stem cell products. Another advantage is reducing the incidence of massive product recalls. This reduction should limit the amount and severity of fallout from episodes such as the recall associated with the Vioxx scandal.[104] The product liability proposal sketched in Part V indicates how to sort out issues of this kind under imperfect information, bounded rationality, and other impediments, but one cannot transpose that sketch into a regulatory key without qualifications and adjustments.

C. Post-Market Regulation

Few lapses are as well-documented as problems with the FDA's post-market drug-safety program and connected regulatory actions.[105] There are many ways in which both the FDA and manufacturers can perform better in the new area of stem cell products than they have in the case of drugs. Once the FDA has approved the marketing of a stem cell product, it should review the performance of that product both in the short term (e.g.,

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INVESTIGATIONAL NEW DRUG APPLICATIONS (2008), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf.

104. On September 30, 2004, Merck & Co. announced a voluntary withdrawal of Vioxx based on data from a prospective, randomized, placebo-controlled clinical trial which showed an increased risk of cardiovascular events, including heart attack and stroke. Press Release, Merck & Co., Merck Announces Voluntary Worldwide Withdrawal of VIOXX® (Sept. 30, 2004) (on file with author); Robert Pear, *Senate Approves Tighter Policing of Drug Makers*, N.Y. TIMES, May 10, 2007, at A1. Additionally, the FDA recommended revised labeling of COX-2 selective and non-selective non-steroidal anti-inflammatory drugs to highlight the potential increased risks of cardiovascular events and gastrointestinal bleeding. U.S. FOOD & DRUG ADMIN., *COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)* (April 7, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm.

105. *E.g.*, U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS (2006); Amanda Gardner, *FDA to Monitor Post-Market Drug Safety*, WASH. POST, Jan. 31, 2007, http://www.washingtonpost.com/wp-dyn/content/article/2007/01/30/AR2007013001388.html. Critics often single out the FDA's delayed response to adverse events and the failure of manufacturers to meet many of their post-market obligations (such as the obligation to conduct safety studies). Curt D. Furberg et al., *The FDA and Drug Safety: A Proposal for Sweeping Changes*, 166 ARCHIVES INTERNAL MED. 1938, 1940 (2006).

in two or three years) and in the long term (e.g., after ten years). It should also require physicians to report adverse events both to the FDA and to manufacturers, and require manufacturers to report adverse events to both the FDA and physicians. Transparency is every bit as important here as it is at the pre-market stage. Furthermore, the FDA should develop clear, effective, and objective criteria and processes for deciding which actions to take when adverse events become known. The FDA might also consider whether, given the many patients who might harbor unrealistic hopes for stem cell products and therapies, to curtail direct-to-consumer advertising for stem cell products insofar as it has the constitutional and statutory authority to do so. As with the pre-market suggestions made earlier, the FDA should tally the anticipated costs to see whether these post-market suggestions are worthwhile.

Once more, CBER is likely to be the FDA center best suited to carry out these actions. There is, however, a wrinkle to this recommendation. As with drugs, there would likely be potential conflicts of interest when the same FDA center that reviews and approves a stem cell product is solely responsible for taking post-market action against the very product it previously approved.[106] Thus, it seems unwise to have the same group in the proposed stem cell department within CBER perform both actions in the case of these products. It would make more sense to structure this department so that two independent groups make pre-market and post-market decisions yet require these groups to collaborate to prevent loss or duplication of expertise.

A pair of problems with post-market regulation merit special attention. One is whether the FDA currently has the expertise and legal power to compel the divulgence of post-market information. In a valuable discussion, Cahoy points out that the FDA has little experience with post-market clinical trials.[107] The FDA's authority to compel such trials is currently limited.[108] Still, the FDA could, under current law, require designers and manufacturers of stem cell products to report adverse events. Although the FDA can recall medical devices, it cannot recall—only seize—drugs and biologics.[109] Stem cell products are highly likely to have a device component. It is therefore an interesting question whether the FDA has the legal power to recall the entire combination product even if it is apparent that adverse events are due solely to the stem cell biologic

106. Furberg et al., *supra* note 105, at 1940.

107. Cahoy, *supra* note 87, at 667; *see* DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GEN., FDA'S MONITORING OF POSTMARKETING STUDY COMMITMENTS 17–18 (2006) (observing that oversight of post-market commitments is not an FDA priority).

108. Cahoy, *supra* note 87, at 667.

109. *Id.* at 668–69.

component rather than the device component.

The other problem with post-market regulation stems from possible perverse incentives. If the FDA requires designers and manufacturers to divulge the results of post-market testing that they have undertaken voluntarily, then in the future they will be less likely to engage in such testing because it increases their liability exposure. And if they do less voluntary testing, the net result might be that less information is available under the FDA requirement than would have been available without it.

Cahoy's "market based" solution to this problem would immunize timely disclosure by limiting the use of regulation-induced information as evidence in product liability cases for failure to warn.[110] He recognizes that this "solution" could grant immunity in some meritorious cases, and that companies might manipulate research outcomes to gain a tort advantage.[111] Cahoy's "second-best" solution would make changes in administrative law. He would heighten the FDA's authority to demand information and allow manufacturers to invoke FDA approval as preempting state tort law.[112] He acknowledges shortcomings with this solution, too. One shortcoming is the FDA's reputation for "organizational dysfunction"[113] in regard to safety. Another lies in the "political issues" related to conducting further trials on a product that the FDA has already cleared for market, as the trials could suggest that the product is not safe.[114]

The upshot is that a sound administrative proposal must reflect an awareness of the ways in which it could backfire. Once these ways have been identified, it becomes a matter of reducing the likelihood and severity of problems associated with demands for more information. One possibility is to see that Cahoy's market-based and second-best solutions need hardly be mutually exclusive. Another possibility is to take into account not only the ancillary risks of regulation but also its ancillary benefits.[115] A third possibility is to be realistic: just because we can anticipate problems does not mean that they will materialize. Similarly, just because we have some effective solutions does not mean that they will work indefinitely. To account for this realistic view, the administrative proposal advanced here is a dynamic approach that calls for adjustment over time. This approach will promote useful innovations in stem cell

110. *Id.* at 657–60.

111. *Id.* at 660.

112. *Id.* at 660–70.

113. *Id.* at 665 (citing INST. OF MED. OF THE NAT'L ACADS., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 79–90 (2007)).

114. *Id.* at 670.

115. Samuel J. Rascoff & Richard L. Revesz, *The Biases of Risk Tradeoff Analysis: Towards Parity in Environmental and Health-and-Safety Regulation*, 69 U. CHI. L. REV. 1763 (2002).

technology.[116]

D. A Risk-Management and Risk-Reduction System

To guide assessments of risk, the observations of Halme and Kessler are highly useful.[117] They classify risks into four separate categories: (1) potential transmission of disease; (2) possible damage or contamination caused by cell processing; (3) potential adverse effects of various cell mixes and different levels of purity and potency; and (4) possible adverse events *in vivo*.[118] In the third category, Halme and Kessler's presentation of risks in terms of cell type, purity, and potency is especially useful.[119]

Once CBER is established as the proper center within the FDA for evaluating stem cell products, the next step in devising a system for managing and reducing the risk of such products is to assemble information about them in a database. Relevant information includes data on clinical trials, pre-market approvals, and post-market developments regarding the risks of various stem cell products. The information should be in the clearest form possible and accessible by at least five different groups: treating physicians; patients; research scientists; designers and manufacturers of stem cell products; and health insurers that are deciding whether stem cell products are covered—either generally in a formulary or on an individual-patient basis.

These groups have different informational needs. Patients who are considering stem cell therapies and products need information that they can understand—say, perhaps, at the level of the Merck Manual or the Mayo Clinic website.[120] In setting up the database, the FDA should consider how best to create a technical database that will be of interest mainly to members of the other four groups and whether to provide a non-technical, patient-friendly database. There would, of course, be no bar to patients accessing the technical database if they wish to do so. From this point, one could leave it to treating physicians to explain the risks and potential benefits to their patients. Differently, one could ask the FDA itself

116. *See supra* text accompanying note 4.

117. Halme & Kessler, *supra* note 77.

118. *See supra* text accompanying note 79.

119. *See supra* text accompanying notes 79, 86.

120. This level will be too high for quite a few patients. *See, e.g.*, Melinda Beeuwkes Buntin et al., *Consumer-Directed Health Care: Early Evidence About Effects on Cost and Quality*, 25 HEALTH AFFAIRS w516, w528 (2006) ("About half of all Americans now have difficulty understanding health information, which could affect their ability to obtain high-quality care."); James C. Robinson, *Health Savings Accounts—The Ownership Society in Health Care*, 353 NEW ENG. J. MED. 1199, 1201 (2005) ("But although some persons can and will function effectively as consumers of health services . . . others will fare less well.").

to set up a second, non-technical database. Among the difficulties the FDA would confront are how to simplify and modify the technical database so that it effectively aids patient decisionmaking, and whether the costs of re-crafting the technical database for patients outweigh the benefits of doing so.

A possible supplement to the information found in an FDA database would be information provided by voluntary organizations. Their information could be funneled into an FDA database as a complement to the more technical information already available. Voluntary organizations in this area tend to be disease-focused nonprofit entities, such as the National Kidney Foundation. As Richard Epstein observes, such organizations frequently fill in information gaps in the medical industry.[121] However, Epstein focuses chiefly on drugs used to treat cancer, and it may be that voluntary organizations will work differently in the case of stem cell products.[122] Surely, though, there is enough public interest in stem cell research, as well as prominent foundations that support this research, to make it plausible that voluntary organizations could be useful sources of information.

The foregoing risk-management and risk-reduction system has both disadvantages and advantages, but with help from voluntary organizations, the advantages win the day. The principal advantages lie in fostering, in different ways, the safety and effectiveness of stem cell products and the decisions to use or avoid them. Manufacturers and scientists can build on the recorded experience with previous research and products. Physicians and patients can work together to select therapies and products with a realistic understanding of the upside and the downside of the choices available. Health insurers can make informed decisions on which therapies and products merit coverage.

The disadvantages of the system are readily apparent; even if the FDA refrains from setting up a non-technical database suited to the average patient, there will still be substantial costs with the technical database aimed at manufacturers, scientists, insurers, and physicians.[123] In light of these costs, the FDA should consider building on the infrastructure of an existing

121. Richard A. Epstein, *Against Permititis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 25–29 (2009).

122. *Id.* at 4.

123. It will be expensive to create and maintain the technical database for all concerned. Serious enforcement and monitoring efforts will likely be necessary for post-market compliance. Failure to make these efforts could lead to underreporting of adverse events and inaccurate risk assessments. *See* Furberg et al., *supra* note 105, at 1939–40 (elaborating on these factors).

U.S. system[124] or at least learn from the experience of other similar international registries, such as the International Stem Cell Initiative Registry or the European Union Human Embryonic Stem Cell Registry. Furthermore, scientists and manufacturers will have legitimate concerns about their patents, trade secrets, patent applications in progress, and other proprietary information. If the type of information and degree of detail required impose substantial burdens on scientists and manufacturers, these burdens might dissuade them from pursuing stem cell products over other biotechnological and biomedical research and products.

E. Relation to Product Liability

If all of the elements of the foregoing proposal are set in place, they should have some impact on manufacturers' liability for stem cell products. But what should be the nature of that impact? An appealing answer is that because stem cell products will have to jump through more hoops to earn approval, manufacturers ought to receive more shelter from product liability than they would have otherwise. This answer, though appealing, is not wholly sound. If the level and degree of regulation of a stem cell product are fairly and accurately adjusted to match its safety risks and its risks of ineffectiveness, then one might argue that those products that are more stringently regulated should receive less protection from product liability suits because of the very fact that they carry elevated risks. Furthermore, manufacturers should not be able to receive increased protection if they have failed to meet all reporting requirements for post-market evidence of ineffectiveness or higher safety risks.

V. A PROPOSED TORT LIABILITY REGIME FOR STEM CELL PRODUCTS

The tort structure I have proposed elsewhere mandates strict liability for products with inadequate warnings or defects, yet adopts measures to safeguard product development and thus encourage innovation.[125] Thus, my product liability proposal contains significant qualifications. These secure a balance among innovation, safety, effectiveness, and patient preferences. This balance is informed by the ethics of imposing risks on others as well as by economic theory. My proposal is mindful of the

124. Examples of relevant systems include the National Library of Medicine clinical trials registry, the FDA's MedWatch Safety Information and Adverse Event Reporting Program, RiskMAPs, the FDA's Adverse Event Reporting System, and the FDA's Postmarket Requirements and Commitments for Human Drugs and Post-Approval Studies for Medical Devices databases.

125. Part V restates the content of Munzer, *supra* note 1, at 145–49, in different but basically equivalent language.

difficulty in determining the causes of harm in the design, development, manufacture, and use of stem cell products. The tort structure advocated here is a seed leaf for making my integrated stem cell proposal generalizable to other problems in which tort law and administrative law intersect.

A. Why Strict Liability Needs to Be Qualified

To begin, a strict liability scheme should include a socialized insurance function to hold down the financial burden on pioneers in the field. Money for a socialized insurance fund would come from patients, designers, and manufacturers. The government would act as an insurer of last resort. One could arrange contributions to the fund in various ways. Perhaps the most straightforward arrangement would have patients pay into the fund for each treatment and firms pay into the fund for each stem cell product. In this scheme, for every stem cell product a firm manufactures, it would pay a fixed amount into the insurance fund. These payments from various sources would defray the costs of caring for those patients who have adverse reactions to stem cell products.

There is every reason to be skeptical of a market-share approach on the producers' side. Under this approach, firms would contribute to the fund based on their market share of all stem cell products or of the stem cell products in a particular category. Nevertheless, a market-share approach may cause inequities in defraying the costs of liability, for some firms may violate standards of safety and effectiveness at the expense of other firms. If these violations occurred, other firms would have an incentive to shave down their compliance with relevant standards, especially if the cost of liability remained relatively low in comparison to the cost of ensuring optimal safety and effectiveness. To avoid these undesirable effects, regulators would have to police compliance with standards and undertake curative measures in cases of noncompliance. It would make little sense to bear the regulatory costs of this work if one can avoid it by the more straightforward approach identified earlier.

The point of my socialized insurance scheme is to spread the cost of liability, but my product liability proposal has additional rules to suppress some of the undesirable effects of an unqualified strict liability regime. These include an unavoidably unsafe rule, a learned intermediary rule, FDA approval as a rebuttable presumption in defective design suits, a state-of-the-art defense, a collateral-source rule, and assorted limitations on damages, especially on punitive damages.

My tort proposal also includes an exception for compassionate use of stem cell products to encourage a balance between patient safety and patient preferences. Patients who are diagnosed with serious or terminal

conditions that lack suitable non-stem cell treatments might want to be treated with cutting edge stem cell products. In such cases, firms should not be held liable for the harms these products cause, even though the stem cell products at issue may be insufficiently tested to warrant putting them on the market generally. Because informed consent is vital to the ethics of imposing risk on patients, I would allow the compassionate use of insufficiently tested stem cell products only when patients were informed of the risks of such use and discouraged from taking inordinate risks.[126] Even then, I would permit use of these products only in serious cases.

The FDA, the patient, and the treating physician should have the main voices in deciding whether a condition is serious enough to warrant a compassionate-use exception. They should also have the main voices in deciding whether safer treatments are insufficiently effective to merit the use of a less well-tested stem cell product. Still, one must be wary of a slippery slope in such decisions. Suppose that an existing treatment is safe and effective—but also very expensive. I doubt that an insufficiently tested but cheaper stem cell alternative treatment should be allowed on grounds of compassionate use. We should avoid the risk of a secondary market developing for stem cell products in which manufacturers both avoid product liability and market these products to patients who are less well-off and less well-informed than most patients.

B. Apportioning Liability in the Supply Chain Under a Strict Liability Scheme

If a stem cell product causes harm, pinpointing the exact cause of that harm can be a serious challenge. First, a stem cell product may become defective at various points in its development. The design may be faulty, the stem cell line may be corrupted, or the manufacture may be shoddy. Next, the product might cause harm when administered to the patient. For instance, medical personnel may improperly dispense or store the product and thereby create or even compound the harm. Further, these scenarios, and many more besides, could combine to produce the harm that results. Unearthing the likely cause of any particular harm may be especially difficult with stem cell products because the use, design, manufacture, and development of these products will be novel. Interplay among these possibilities might aggravate the task of identifying the causes of the harm a patient suffers.

126. *See, e.g.*, Zubin Master & David B. Resnik, *Opinion: Reforming Stem Cell Tourism,* THE SCIENTIST, Sept. 14, 2011, http://the-scientist.com/2011/09/14/opinion-reforming-stem-cell-tourism (offering suggestions for thwarting the use of unproven and possibly harmful stem cell therapies); *cf.* the discussion of Regenexx-C *supra* at text accompanying notes 55–66.

For this reason, my qualified strict liability scheme explores collective and proportional liability theories.[127] Under these theories, plaintiffs would be allowed to recover damages against multiple members of the supply chain in situations where fault could not be satisfactorily shown as to any one party. Proportional liability would parcel out the cost of liability based on the degree of harm each of the defendants caused. Members of the supply chain would be free to allocate the costs of liability among themselves, such as through indemnification arrangements. They could also minimize their collective risk through self-regulation.

In some cases, the party responsible for the harm may be uniquely identifiable. For instance, if a design is faulty, the plaintiff may bring suit against the design firm. Likewise, depending on the harm, a lawsuit may be brought for a manufacturing defect against the manufacturer or for an inadequate warning against either the manufacturer or designer. Each type of lawsuit presents distinct challenges.[128] As to the first option, a defect in design may create liability if there were safer design alternatives available at the time the product was conceived. If no such design existed, designers ought to be able to avoid liability with the state-of-the-art defense. The second option—suing the manufacturer—would be potentially more lucrative for plaintiffs, since manufacturers would rarely have a state-of-the-art defense. As to the third option, a lawsuit for inadequate warnings should fail in most cases if the warnings were transparent, but such warnings could increase the potential liability for designers and manufacturers, and thus reduce their incentive to unearth adverse information.[129] To avoid this result, courts could create protections for early warnings, but afford no such protections for delayed warnings.

VI. INTEGRATING ADMINISTRATIVE AND PRODUCT LIABILITY LAW

Accepting my administrative proposal does not require acceptance of my product liability proposal, nor does accepting my product liability proposal require acceptance of my administrative proposal. However, the two proposals are consistent with each other. Moreover, they are complementary, well-suited to each other, and mutually reinforcing. As to integration, the nub of the matter is to clearly specify *how* they interact on these criteria. That is the first item on the agenda of this Part. The second is to show how the results can be extended to other areas of tort and

127. *E.g.*, Allen Rostron, *Beyond Market Share Liability: A Theory of Proportional Share Liability for Nonfungible Products,* 52 UCLA L. REV. 151 (2004).

128. Tomas J. Philipson & Eric Sun, *Is the Food and Drug Administration Safe and Effective?*, 22 J. ECON. PERSPECTIVES 85, 90–91 (2008).

129. *See supra* text accompanying notes 87–88, 108–15.

administrative law.

A. How the Two Proposals Mesh with Each Other

Stem cell products have risks that are largely unknown and potential rewards that are highly touted. The tort and administrative proposals detailed in this Article share some aims and means for reducing the risks of stem cell products while permitting their relatively unencumbered development. To explain how the commonalities between these proposals enable them to mesh well together, it is necessary to clarify three key terms, which I use in a semi-technical way.

Two proposals are *complementary* if they work together to promote common aims. The proposals advanced here share the following aims: mitigating disincentives to enter the stem cell market; increasing the safety of stem cell products and thereby lowering the risks they pose to consumers; and promoting the effectiveness of stem cell products and thereby increasing their usefulness to consumers.

Two proposals are *well-suited* if they use the same or similar means to achieve their shared aims with as little waste as possible of resources expended on extraneous means and aims.

Finally, two proposals are *mutually reinforcing* if each encourages compliance with the other. Take note that writing of means, aims, incentives, and avoiding waste does not make either proposal, or both of them together, a wholly consequentialist affair. The best analyses of risk reduction, risk management, and risk imposition have an important non-consequentialist cog in that they take seriously the ethics of imposing risks on other people.[130]

1. Complementarity and Common Ends

a. Entry

The product liability proposal mitigates disincentives to enter the stem cell market. It thereby advances safety in two ways. First, it immunizes firms that disclose post-market test results from liability in inadequate warning lawsuits. The disclosure must be timely, but such prompt notice enables designers and manufacturers to limit liability, which offers the prospect of increased profits. Secondly, the proposal limits punitive damages for firms that have fully complied with all FDA requirements. This limitation reduces the monetary risks of designing and making stem cell products. Lowering the exposure to one category of damages should

130. *See generally* Munzer, *supra* note 1.

draw more firms into the market. It should also increase the quality and variety of stem cell products, which might help control prices for consumers. Thus, limiting liability, and in turn reducing barriers to entry, increases the incentive to disclose post-market test results and to comply fully with all FDA requirements that advance safety.

The administrative proposal also mitigates disincentives to enter the stem cell market in various ways and thereby promotes safety. To begin, it eliminates the lobbying that would otherwise be needed to slot a proposed stem cell product into a particular FDA center. Under current law, firms often hire lawyers or professional lobbyists to persuade the FDA to place their products into a center that tests, or at least is believed to test, less rigorously and less expensively than another center. The proposal eliminates this lobbying expense by having a single department within CBER evaluate all proposed stem cell products.

Some might contend that the mandatory insurance provision in the product liability proposal will greatly increase barriers to entry and thereby raise prices to consumers. However, this assertion is easily rebutted. All insurance costs something. If it did not, there would be no reason for the insurer to provide any coverage. For designers and manufacturers of stem cell products, buying insurance is a way to hedge against risk. Hence, a required insurance premium, while possibly representing a minor barrier to entry, provides an even greater demonstrable benefit that reinforces the complementary nature of the product liability and administrative proposals. The mandatory insurance provision thus serves to mitigate disincentives to enter the stem cell market.

Further, the mandatory insurance premium is based partly on market share. Thus, a firm hoping to break into the field will face relatively small insurance costs. In return for a modest premium, the firm cabins the risk of debilitating judgments and settlements. Thereafter, efforts to improve safety and effectiveness, the eventual success of those efforts, compliance with post-market regulations, and the securing of FDA approval will all play a role in decreasing firms' payments into the mandatory insurance fund. As with all insurance, the premium paid hedges against risk, and that hedge should appeal to almost all firms, large and small. Consequently, the mandatory insurance provision in no way shows that the two proposals fail to mitigate disincentives to enter this market. As a result, any effect on costs to consumers stemming from the mandatory insurance provision is likely to be modest.

b. Safety

The two proposals are also complementary because they work together

to increase the safety of stem cell products and thereby decrease the risks to consumers. The product liability proposal advances this end by incentivizing firms to follow FDA procedures that will likely make their products safer by limiting liability and punitive damages in exchange for compliance. Further, FDA approval of products results in a rebuttable presumption of safety so far as design flaws are concerned. The availability of this presumption should encourage firms to comply with FDA regulations. As a corollary, compliance with FDA regulations might lead to a reduction in the insurance premiums paid by firms.

The administrative proposal seeks to increase the safety of stem cell products through its risk-reduction and risk-management system. This system provides for the rapid dissemination of information among firms, doctors, patients, consumers, and the FDA. The heightened level and quality of information should enable all concerned to make better choices about the design, manufacture, and use of stem cell products. In this situation, better choices include safer choices.

Two primary objections exist to the argument for complementarity. The first is that various parts of the product liability proposal actually increase risk to consumers. Limits on punitive damages might lead to carelessness on the part of designers and manufacturers. Immunizing defendants in failure-to-warn suits because of timely disclosure of post-market test results lowers the deterrent value of product liability suits. This lower value in turn decreases consumers' prospects of financial recovery. The objection, if sound, might suggest that the product liability proposal is not complementary to the administrative proposal, as the former undermines the aim of increasing safety and decreasing risk to consumers.

However, analysis of this objection reveals that it is less incisive than it initially appears. For a start, the objection relies on a suppressed premise—namely that many, if not most, parts of the product liability proposal increase consumer risk. Without this premise as a base, to be convincing the objection requires extrapolation from the few parts mentioned in the preceding paragraph to all or most parts of this proposal. Such an extrapolation is patently unwarranted, for it is evident that the proposal contains many provisions that increase consumer safety. Among them are tort liability for defective products and inadequate warnings and the fact that the regime suggested is a modified strict liability regime for stem cell products. Precisely because the extrapolation is unwarranted and the suppressed premise is false, many, if not most, parts of the proposal advance consumer safety.

A further point has to do with the "part-to-whole" relationship contemplated by the first objection. One way of putting the objection is that some elements of the product liability proposal undermine safety, or at

least seem to do so. This is the "part." From this point, the objector reasons that the proposal overall undermines safety. This is the "whole." This reasoning is fallacious. What is true of a part, or even of several parts, need not be true of the whole. It could well be that the proposal overall advances safety. So it is not simply that the suppressed premise is false and the extrapolation is unwarranted that the proposal advances safety; it is *because* the suppressed premise is false and the extrapolation is fallacious that the overall proposal could advance safety.

Moreover, both proposals seek to take competing considerations into account. On the one hand, were safety standards raised to an unattainable level, fewer firms would place even a toe in the icy waters of the market. On the other hand, were regulations decreased or loosened and tort actions curtailed, the prospect would arise of a free-for-all market in which firms cut costs and put out substandard products. Although some balancing is in order, it is too blunt to turn the entire conversation into "weighing" things on "scales." A virtue of much sophisticated work in moral and political theory is the move away from sole reliance on crude balancing metaphors to a wider awareness of the ways in which reasons and normative considerations on one side can variously exclude, undercut, override, neutralize, or otherwise affect reasons and normative considerations on the other.[131]

At the intersection of the two proposals, then, we must be wary certainly of tipping the scale too far in either direction. But we must be equally wary of allowing one proposal to exclude, or otherwise undercut, the other to an indefensible extent. Once these points are taken to heart, we see that the liability proposal must not be pushed so far as to throw the administrative proposal out of balance or to derail it. The parts of the liability proposal that the objection invokes fall well short of an exhaustive list of its parts. Other parts provide a good many incentives to safety. Consequently, once a judicious merger of Parts IV and V is reached, the fact that some aspects of the product liability proposal might result in less than an extremely high level of consumer safety does not defeat the complementarity of the proposals as regards safety.

The second objection is that the various incentives to follow FDA procedures, in the hope of avoiding product liability or at least punitive damages, might not increase consumer safety. The claim that it increases

131. *See generally* 1 DEREK PARFIT, ON WHAT MATTERS 31–174 (2011); JOSEPH RAZ, BETWEEN AUTHORITY AND INTERPRETATION: ON THE THEORY OF LAW AND PRACTICAL REASON 6–8, 143–47, 186–87, 205–08, 214–19, 367–69 (2009); JOSEPH RAZ, PRACTICAL REASON AND NORMS 35–48 (3d ed. 1999); Robert Nozick, *Moral Complications and Moral Structures*, 13 NAT. L. FORUM 1 (1968).

safety, it might be said, depends on the idea that the FDA has special knowledge about stem cell products. Only with this special knowledge can the FDA assess accurately the safety of products submitted for its approval. Yet, the objection concludes, right now the FDA has no such expertise or special knowledge.

This objection raises a problem that the administrative proposal is designed to overcome or at least to limit. It will take some time for the new department within CBER to gain knowledge of stem cell products. But it will likely not take long, for in the past two decades graduate schools in the life sciences have been minting new scientists with doctorates in stem cell biology. Hence, there should be a good labor supply of qualified scientists.

Moreover, the proposal deals with the timing issue by instituting various requirements that must be met before the limit on punitive damages takes effect. One such requirement is that the FDA have a more accurate picture of the risks of stem cell products. So before the limits on product liability damages come into effect, stem cell technology must be well-enough studied for the FDA, designers, manufacturers, physicians, and consumers to have a decent grasp of the risks. In consequence, the objective of consumer safety has priority over mitigating the disincentives to enter the market.

Hence, when the incentives to follow FDA procedures do take effect, the specialized knowledge of the FDA will enable compliance with the FDA procedures to increase consumer safety. Granted, this point does not entail that safety will increase immediately. Still, the modest limits on liability, preclusion of punitive damages, and significant barriers to entry are likely to have two effects. One is to encourage independent safety protocols by manufacturers and regulators. The other is to give the FDA time to come up with well-vetted procedures for increasing safety.

Although one can imagine why a legal scholar might make one or the other of the two objections above, it would be downright odd to make them together. The first objection targets the product liability proposal by claiming that it decreases consumer safety. The second targets the administrative proposal by claiming that it decreases consumer safety. If both objections were sound, that would hardly show that the proposals are not complementary. In fact, both proposals would be superlatively complementary because they would work together to lower consumer safety—perverse though such an aim would be. Perhaps some might hurl as many objections as possible in hopes that at least one will stick. In any case, the foregoing replies establish that neither objection is well-taken and that the two proposals are complementary as to safety.

c. Effectiveness

Here the product liability proposal plays a minor role, for consumers can hardly sue in tort just because a particular stem cell product failed to help them. Still, consumers might be able to sue manufacturers for false or misleading advertising. Also, the regime of modified strict liability encourages designers and manufacturers to avoid unnecessary risks and to produce products that work well. In these ways, the tort proposal thus furthers effectiveness to some extent.

The administrative proposal carries the laboring oar for effectiveness. Under it, the FDA will approve only products that clinical trials have shown to be effective for a given injury, disease, or condition. Additionally, if post-market testing indicates that certain products are ineffective, or are less effective than alternatives that have better-known risk profiles, then ineffective products will be withdrawn from the market, and less effective products with decent alternatives will decline in market share. Thus, the two proposals are complementary not only with respect to safety and mitigating disincentives to enter the stem cell market but also with respect to effectiveness.

2. Well-Suitedness and Common Means

Complementarity has to do with ends; well-suitedness concerns means. Recall that two proposals are well-suited if they use the same or similar means to achieve their shared ends with as little waste as possible of resources expended on extraneous means and ends. Two features of my proposals illustrate how well-suited they are to each other. The risk-management system created for the FDA is used in product liability cases. And the early disclosure of post-market test results both brings stem cell products into compliance with suggested FDA regulations and shields against some sorts of product liability lawsuits.

a. Risk-Management System

The system advocated in the administrative proposal includes a database of stem cell products that contains, among other things, information on their safety and effectiveness.[132] The contents of the database include information secured by post-market testing. By having this information readily accessible, the database makes it easier to determine the insurance premiums to be paid for various stem cell products in light of their claims histories. From the database, the entity overseeing the product liability

132. *See supra* text accompanying note 120.

insurance fund has an easier road to determine the market share of various firms. Thus, both proposals employ the same or similar means to further the aims of safety and effectiveness. These means might also advance the aim of mitigating disincentives to enter the stem cell market by calibrating mitigation. The two proposals are well-suited to each other, for the database included in the risk-management system aids both the administrative and product liability schemes in achieving their similar objectives.

b. Disclosing Post-Market Test Results

The product liability proposal uses incentives for firms to disclose post-market test results even when, and especially when, they are unfavorable to the firms' products. The administrative proposal compels such disclosure. Here, similar means advance the ends of having safe and effective stem cell products.

Precisely how the two proposals interlock here is slightly complicated. Insofar as the FDA has the legal authority to compel the disclosure of post-market test results, the so-called transparency paradox forcefully emerges.[133] To combat the possibility of backfire—having less information rather than more as a result of regulation—the qualified strict liability regime limits the information that plaintiffs can use in inadequate-warning suits.[134] The product liability proposal would also limit punitive damages.[135] Hence, this proposal has ways to encourage speedy disclosure by firms of post-market test results. The two proposals are well-suited in that both use similar means to advance the ends of safety and effectiveness.

Let no one contend that a combination of carrot, via the product liability proposal, and stick, via the administrative proposal, is unnecessary. The idea behind such a contention seems to be that incentivizing something while also compelling it is exactly what makes the two proposals ill-suited, or, at least, redundant. I reply that here we need both carrot and stick.

With only the stick, firms might well cease, or curtail, post-market testing for fear of product liability. With only the carrot, some firms might choose not to comply with the FDA. Noncompliance might be the result of calculating either that the costs of disclosure outweigh the benefits or that the unfavorable information is unlikely to be discovered by anyone else. Either way, the consumer is left at a higher risk of using an unsafe or ineffective product. What may seem superfluous is in fact necessary. The two proposals should use the common means of disclosure to pursue ends of

133. *See supra* text accompanying notes 87–88, 107–14.
134. *See supra* text accompanying notes 125–27.
135. *Id.*

safety and effectiveness.

3. Mutual Reinforcement

Two proposals are mutually reinforcing if each encourages compliance with the other. We have already seen one instance of mutual reinforcement: disclosure of post-market testing as mandated by the FDA reinforces—and is reinforced by—the corresponding immunity given in product liability litigation. Here are three more examples.

a. Rebuttable Presumption of Safety

Under the administrative proposal, FDA approval gives designers a rebuttable presumption of safety in product liability suits. The product liability proposal, by giving designers some protection against strict liability, spurs them to comply with FDA regulations for approving a stem cell product. Further, the rebuttable presumption of safety is bolstered by, and partly justified on the basis of, stricter FDA approval standards that increase consumer safety. Thus the added difficulty in securing FDA approval should erase doubts that the presumption might compromise consumer safety.

b. Limits on Punitive Damages

The punitive damages limit and compliance with the suggested FDA regulatory scheme mutually reinforce each other. The product liability regime, by limiting firm exposure to punitive damages, offers an incentive for firms to adhere to FDA regulations. In turn, strict FDA regulations are warranted partly because compliance with them limits the damages that injured plaintiffs can recover.

c. Risk Management and Socialized Insurance

The administrative proposal includes a risk-management system. This system, with its database, facilitates the exchange of information among the FDA, designers, manufacturers, physicians, and patients.[136] The transparency of the system gives firms an incentive to participate honestly. The product liability proposal includes a socialized insurance scheme. Firms' premiums are partly a function of information about the safety and effectiveness of their products. Honest participation in the risk-management system is likely to hold down the amount of their insurance premiums. Consequently, the socialized insurance scheme provides

136. *See supra* text accompanying notes 119–20.

incentives to participate honestly in the risk-management system and to comply with FDA regulations pertaining to safety and effectiveness.

Only Pollyanna, some might say, would have such an optimistic view of the honesty of designers and manufacturers.[137] They are likely, some would say, to provide *false* information. To a significant extent, I disagree. By no means am I blessed with the constant sincerity and sunny disposition of the title character in Porter's novel. Yet I think that the penalties for false statements by designers and manufacturers, aided by the transparency of the system in which they work, is apt to induce honest participation and significant, if grudging, compliance with FDA regulations.

The whole of the mutual reinforcement argument can be seen by looking at the above examples in the aggregate. The prospect of having to pay large judgments or settlements in a stem cell product liability suit may lead even the most safety-conscious firms to think twice about entering the stem cell market. By encouraging compliance with strict FDA regulations, the two proposals work together to increase safety and lower the chance that firms will be hit by an enormous verdict despite meticulous research and development. The rebuttable presumption of safety that arises from FDA approval further lowers the chances that firms will be exposed to substantial liability. The limit on punitive damages resulting from compliance with FDA procedures protects firms against debilitating damage awards even if a verdict is returned against it. Conversely, the socialized insurance premiums reflect, in their amounts, regulatory compliance. Should all firms comply with FDA regulations, it becomes even more appropriate that socialized insurance ought to exist to prevent any one firm from financial ruin.

To sum up: these four examples, as components of proposals for two different areas of the law, show that the proposals mutually reinforce each other in encouraging increased safety and effectiveness pursuant to FDA regulations by way of limiting potential liability and mitigating disincentives to market entry.

B. Generalization and Its Limits

Think of the integration of administrative and product liability law in Part VI.A as a wrench. Just because one has a wrench does not mean that every problem is a bolt that needs tightening. It would be foolish to claim that the integration suggested here can be applied without change to every area in which administrative law and product liability intersect. Here I argue that my integrated proposal, with adjustments, can be helpful in at

137. *See generally* ELEANOR H. PORTER, POLLYANNA (1913).

least some other cases.

To show that I do not see all problems as bolts, I emphasize that the integrated proposal is unlikely to be particularly helpful or even necessary for most workplace risks and injuries. Workers compensation and the Occupational Safety and Health Administration (OSHA) handle the majority of such cases fairly well. Nor is the proposal apt for problems of climate change. There are so many causes of climate change, and the ramifications and remedies are so disputed and so in need of international cooperation, that this Article can throw little light on them.

Nevertheless, the integrated proposal illuminates the regulatory and liability issues involved in toxic substances and nanotechnology.

1. Toxic Substances

Regulatory agencies and the judicial system do not work together to form a cohesive scheme in the case of toxic substances. Despite *Chevron*,[138] a court can still discard agency actions that do not meet the court's scientific standards.[139] The *Chevron* standard is sufficiently amorphous in practice that a court can strike down agency regulations because it disagrees with the agency's science. Moreover, compliance with judicial decisions can interfere with an organization's ability to comply with regulations. Sometimes judicial orders are so cumbersome that they frustrate regulatory compliance.[140] In this area, the actions of courts and administrative agencies are not complementary, well-suited, and mutually reinforcing.

All the same, at least two features of the integrated stem cell proposals can be mapped onto the case of toxic substances, for both stem cells and toxic substances have problems with uncertainty and risk. First, a presumption of safety with agency approval after full disclosure by the regulated entity would help to fix the current problem of judicial rejection of agency risk assessments. The Environmental Protection Agency (EPA), OSHA, and the FDA have scientific competence and already have a hand in pre-market approval and regulation.[141]

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138. Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 843–44 (1984) (setting an "arbitrary [and] capricious" review standard when an agency is charged with regulating a particular problem).

139. *See* Gulf S. Insulation v. U.S. Consumer Prod. Safety Comm'n, 701 F.2d 1137, 1145–50 (5th Cir. 1983) (holding that the Commission's method of determining carcinogenicity was insufficiently precise and had too high a margin of error); CARL F. CRANOR, REGULATING TOXIC SUBSTANCES: A PHILOSOPHY OF SCIENCE AND THE LAW 110–11 (1993).

140. CRANOR, *supra* note 139, at 111.

141. *Id.* at 105–07. The agencies have authority to regulate toxic substances under scattered sections of the Toxic Substances Control Act, 15 U.S.C. §§ 2601–92 (2006); the

Second, the risk-management system and risk-reduction system proposed in Part IV.D of this Article would, in principle, work well for toxic substances. Current administrative schemes concentrate heavily on consumer safety, and some post-market regulations already exist. Even if the statutes cited favor companies that have passed pre-market approval,[142] the favor does not extend to tort suits so that companies can hide post-market test results without fear of liability. As Part IV.C shows, mandatory post-market testing and the rapid dissemination of information serve the goal of consumer safety. Disclosing the results of post-market testing and the effects of consumer use would be a ground for limiting product liability, and thus would be an incentive for companies to disclose.

Nevertheless, I do not claim that the integrated proposals advanced here are wholly appropriate for toxic substances. For a start, the socialized insurance function in the case of stem cells is not readily transferrable. Perhaps it is plausible to believe that many stem cell products will have similar risks and unknowns, and that adverse events will be seen in patients fairly quickly. The risks and unknowns of toxic substances run the gamut from relatively benign (aspartame) to extremely dangerous (asbestos). Adverse consequences might not come to light for many years (asbestos). Furthermore, incentives are not likely to operate in the same way. Scientists and physicians are aware that the side effects of stem cell products are unknown, and for that reason have an incentive to withhold them from patients until they are reasonably confident of a promising outcome. In contrast, firms put new chemicals into use without enormous concern for consumer safety. Because most chemicals do not have dangerous effects, the firms have little incentive to delay their introduction.

2. Nanotechnology

The nanotechnology field is similar to the field of stem cell products in key respects. For starters, both have significant potential to improve health. Nanotechnological research has come up with new diagnostic tests,[143] therapeutic vehicles,[144] and antibiotics for drug-resistant pathogens,[145] to

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Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. §§ 136–136y (2006); and the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–99 (2006).

142. *See supra* note 141; CRANOR, *supra* note 139, at 104–08.

143. Kevin Rollins, *Nanobiotechnology Regulation: A Proposal for Self-Regulation with Limited Oversight,* 6 NANOTECHNOLOGY L. & BUS. 221, 223 (2009).

144. *See generally* Robert Lam & Dean Ho, *The Coalescence of Nanotechnology with Systems Biology for Optimized Drug Delivery*, 5 NANOTECHNOLOGY L. & BUS. 125 (2008) (discussing developments in drug delivery systems and their relationship to nanotechnological research).

145. Kerriann Greenhalgh & Edward Turos, *In Vivo Studies of Polyacrylate Nanoparticle Emulsions for Topical and Systemic Applications*, 5 NANOMEDICINE: NANOTECHNOLOGY, BIOL. &

name only a few.[146] Next, the risks of using both nanoparticles and stem cell products are unknown and difficult to quantify.[147] Even silver and gold take on new and sometimes unpredictable properties when reduced to the nanoscale.[148] Finally, as with stem cells, neither regulatory agencies nor tort law doctrine consider nanoparticles to be worthy of separate and special consideration.[149]

Given these similarities, at least some features of my integrated proposal for stem cells would be useful in the nanotechnology context. The socialized insurance function is one such feature. Although consumers and manufacturers should bear some of the risks and costs, at some point government-backed insurance as a last resort will be appropriate for nanotechnology products with unknown and unpredictable risks. Here, proportional liability based on market share can also be helpful in calculating initial manufacturer liability. Of course, once unknown risks become known and predictable, this part of the integrated proposal should be reassessed—just as it should in the case of stem cells.

Keep in mind that nanotechnology, like stem cell products, merits incentives because large social benefits are in the offing. Limiting punitive damages and allowing some litigation protection in failure-to-warn cases when a risk has been disclosed early should help prompt manufacturers to enter the field. By protecting nanotechnology firms from huge judgments, one can spur post-market research and disclosure of newly discovered risks. These provisions of the integrated proposal are especially apt in the case of nanotechnology that has significant potential to benefit others. I would not press them into service for, say, nanotechnology-based cosmetics.

And, yet, it is hardly sound to map all features of the integrated proposal onto nanotechnology. For one thing, the regulatory picture is much more complicated. Stem cell products will be mainly, if not entirely, the province of the FDA. Nanotechnology is under the sway not only of the FDA but also the EPA, OSHA, the Department of Agriculture, and other agencies. This multi-agency approach makes sense because nanotechnology is already being used in energy, optics, electronics, and environmental

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MED. 46 (2009).

146. For a list of other uses, see Rollins, *supra* note 143, at 222–24.

147. *See* THE NANOTECHNOLOGY CHALLENGE: CREATING LEGAL INSTITUTIONS FOR UNCERTAIN RISKS (David A. Dana ed., 2012) (collecting assorted essays on nanotechnology); David W. Grainger, *Nanotoxicity Assessment: All Small Talk?*, 61 ADVANCED DRUG DELIVERY REVS. 419 (2009) (discussing technical details that contribute to the difficulty of predicting nanotoxicity).

148. Jessica K. Fender, Note, *The FDA and Nano: Big Problems with Tiny Technology*, 83 CHI.-KENT L. REV. 1063, 1068 (2008).

149. Rollins, *supra* note 143, at 237–39.

remediation.[150] Furthermore, even the picture within the FDA is more complicated. CBER and the Office of Combination Products are the right places for evaluating stem cell products. Yet the FDA currently studies and regulates nanotechnology through CDER, CDRH, the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, and the National Center for Toxicology Research.[151] The FDA has formed a Nanotechnology Task Force to "identify and recommend ways to address any knowledge or policy gaps that exist so as to better enable the agency to evaluate health effects from FDA-regulated products that use nanotechnology materials."[152] Nanotechnology requires a much more thorough revamping of the FDA than do stem cell products.[153] It also requires a multi-agency approach that is inapposite to the case of stem cells.

CONCLUSION

The possibilities of stem cell products in treating disease and in regenerative medicine are vast. These possibilities, though, come with significant risks. It would be regrettable to delay the needed reformation of administrative law until hundreds, if not thousands, of stem cell products are on the market. The administrative regulation of eventual stem cell products by the FDA will require exacting attention to safety and effectiveness without imposing an undue burden on manufacturers. The same is true for product liability claims regarding stem cell products. Alas, no existing category—whether vaccines or blood products or combination products—offers a perfect legal model for stem cell products. However, one can tease out pertinent features of these categories to show what might work well for stem cell products. These features can then be considered and molded into more definitive recommendations as these products appear on the market and their risks and rewards become better understood over the coming decades.

150. Gregory Mandel, *Nanotechnology Governance*, 59 ALA. L. REV. 1323, 1331–40 (2008).

151. Rollins, *supra* note 143, at 227.

152. U.S. FOOD & DRUG ADMIN., *Nanotechnology Task Force: About the Task Force*, http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm2006658.htm (last visited Nov. 30, 2012).

153. For further commentary, see Mark N. Duvall, Alexandra M. Wyatt & Felix S. Yeung, *Navigating FDA's Approach to Approval of Nanoparticle-Based Drugs and Devices*, 8 NANOTECHNOLOGY L. & BUS. 226 (2012); Jordan Paradise, *Reassessing Safety for Nanotechnology Combination Products: What Do Biosimilars Add to Regulatory Challenges for the FDA?*, 56 ST. LOUIS U. L.J. 465 (2012).