ORAL ARGUMENT NOT YET SCHEDULED

CASE NO. 12-5254

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

REGENERATIVE SCIENCES LLC, et al.
Appellants,

v.

UNITED STATES OF AMERICA,
Appellee.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

CASE NO. 1:10-CV-01327-RMC

FINAL BRIEF FOR THE APPELLANTS

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March 15, 2013

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28(a)(1), counsel for the Appellants certify as follows:

A. Parties and Amici

This is a direct appeal for review in this Court of two final orders of the United States District Court for the District of Columbia. The Plaintiff before the District Court was the United States of America. The Defendants before the District Court were: 1) Regenerative Sciences LLC; 2) Christopher J. Centeno M.D.; 3) John R. Schultz M.D.; and 4) Michelle R. Cheever. Amici before the District Court were: 1) the Association of American Physicians and Surgeons, Inc.; and 2) the American Association of Orthopaedic Medicine.

The Appellants in this Court are: 1) Regenerative Sciences LLC; 2) Christopher J. Centeno; 3) John R. Schultz; and 4) Michelle R. Cheever. The Appellee in this Court is the United States of America. There are two *amicus curiae* before this Court: 1), the Association of American Physicians & Surgeons; and 2) the American Association of Orthopaedic Medicine.

Appellant Regenerative Sciences LLC. ("Regenerative") is a closely held nongovernmental corporation with no parent company. No publicly-held company has a 10% or greater ownership interest of its shares. Regenerative, by and through physicians licensed to practice medicine in the State of Colorado, performs a

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variety of non-surgical procedures for patients suffering from moderate to severe joint, muscle, tendon, or bone pain due to injury or their conditions. One such procedure, known as the Cultured Regenexx Procedure, is the subject of the litigation and the underlying decision from which this appeal arises.

B. Rulings Under Review

Appellants appeal from the Memorandum Opinion and Order of Permanent Injunction entered July 23, 2012 by the District Court (Collyer, J.) (DE 47; Addendum 1; JA 924-945; DE 48; Addendum 2; JA 946-957).

C. Related Cases

This case has not previously been before this Court. Counsel is not aware of any related cases within the meaning of Circuit Rule 28(a)(1)(C).

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TABLE OF AUTHORITIES[1]

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[1] Authorities upon which we chiefly rely are marked with asterisks

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GLOSSARY

cGMP: Current Good Manufacturing Practices

FDA: United States Food & Drug Administration

FDCA: Federal Food Drug & Cosmetic Act; 21 U.S.C. § 301, *et seq.*

HCT/P: Human cells, tissues, or cellular or tissue-based products; 21 CFR § 1271.3(d)

PHSA: Public Health Service Act; 42 U.S.C. § 201, *et seq.*

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JURISDICTIONAL STATEMENT

Plaintiff/Appellee United States of America invoked the jurisdiction of the District Court under 21 U.S.C § 332(a) and 28 U.S.C. §§ 1331, 1337 and 1345. On July 23, 2012, the District Court entered summary judgment in favor of the United States, dismissed the Counterclaims of the Defendants, and permanently enjoined the Defendants pursuant to 21 U.S.C. § 332(a). (DE 47; Addendum 1; JA 924; DE 48; Addendum 2; JA 946).

The District Court's Memorandum Opinion and Order of Permanent Injunction were final and disposed of all of the parties' claims and defenses; *see* Order, (DE 49). Defendants filed their Notice of Appeal on August 7, 2012. (DE 50; JA 958). This Court has jurisdiction pursuant to 28 U.S.C. § 1291.

STATEMENT OF ISSUES PRESENTED FOR REVIEW

I. Whether the District Court Erred in Granting Summary Judgment for the Government.

II. Whether the District Court Erred in Dismissing the Appellants' Counterclaims.

III. Whether the District Court Erred in Permanently Enjoining the Appellants.

STATUTES AND REGULATIONS

Copies of pertinent statutes and regulations are attached hereto as an addendum.

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STATEMENT OF THE FACTS

I. INTRODUCTION[2]

Before the Government filed its Complaint against Regenerative Sciences LLC ("Regenerative"), Dr. Christopher Centeno, Dr. John Schultz, and Ms. Michelle Cheever[3] (hereinafter "the Appellants"), the Appellants treated the musculoskeletal injuries of their patients at the Centeno-Schultz Clinic in Broomfield, Colorado using, *inter alia*, a medical procedure known as the Cultured Regenexx Procedure (hereinafter, "the Procedure").[4] As the District Court found,

> Drs. Centeno and Schultz practice together and jointly own the Centeno-Schultz Clinic in Broomfield, Colorado. Drs. Centeno and Schultz are also the majority shareholders of Regenerative, which owns the Regenexx Procedure and exclusively licenses the Clinic to use it. Ms. Cheever (sic) serves as Regenerative's Laboratory Director. Regenerative and the Clinic are related companies and operate as one business.

(DE 47:2; Addendum 1; JA 947) (Memorandum Opinion, at 2.).

We explain the regulatory regime governing the Procedure, and the details of the Procedure itself, in the following sections of this Statement of Facts.

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[2] Record Citation will be in the following format: (DE. [Docket Entry Number]:[Page or Paragraph Number]; Addendum [Addendum Number]; JA [Deferred Joint Appendix Page Number]).

[3] Ms. Cheever is no longer employed by Regenerative but remains an appellant in this case.

[4] Here, we use the term "Cultured Regenexx Procedure" to distinguish it from Regenerative's other Regenexx procedures which do not involve the culture expansion of cells. No other Regenexx procedure is at issue in this case.

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II. THE PART 1271 REGULATIONS

The regulations at issue in this case are found at 21 C.F.R. Part 1271. The FDA drafted these regulations pursuant to authority delegated by Congress at 42 U.S.C. § 264, which provides in pertinent part as follows:

> The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.

42 U.S.C. § 264(a); *see* 63 Fed.Reg. 26745 (May 14, 1998).

The Government has charged that the Procedure constitutes the manufacturing of a "Human cell, tissue, or cellular or tissue based product" (hereinafter "HCT/P") which is defined as an "article[] containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer ***into a human recipient***." 21 C.F.R. § 1271.3(d) (emphasis added).

The HCT/P definition does not distinguish between whether the "human recipient" is receiving the HCT/P from another person (an "allogeneic" procedure) or whether the "human recipient" is receiving the HCT/P from himself (an "autologous" procedure). However, the 1271 regulations themselves "do not require manufacturers to determine the eligibility of donors for cells or tissues for autologous use." (DE 20:38-39) (Motion to Dismiss at 38-39; *citing* 21 C.F.R. §

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1271.90(a)(1)). As the FDA has itself articulated, "the risk of disease transmission from such activities is believed ***minimal***" and thus communicable disease testing is not necessary." 64 Fed.Reg. 52715; (emphasis added).

At 21 C.F.R. § 1271.10, FDA has created what it describes as a "risk based, tiered approach" to the regulation of HCT/Ps; 63 Fed.Reg. 26745. Pursuant to that regulation, HCT/Ps must satisfy a four-part test in order to be regulated "solely by controlling the infectious disease risks they present through the [Part 1271 regulations]…." (DE 1:¶26; JA 16) (Complaint at ¶26). The only prong of that test at issue in this case is that the HCT/P be "minimally manipulated." 1271.10(a)(1). In other words, in order to be regulated solely by the Part 1271 regulations (and not as drugs, devices or biological products as set forth in 21 C.F.R. § 1271.20), HCT/Ps must be minimally manipulated.

As it relates to cells and nonstructural tissue, FDA defines "minimal manipulation" as "processing that does not alter the relevant biological characteristics…" 21 C.F.R. § 1271.3(f). No regulation defines "relevant biological characteristics."

In the case below, the Government charged that the Procedure constituted the more-than-minimal-manipulation of HCT/Ps and was therefore subject to regulation as a drug or biological product. (DE 1:¶29; JA 17). The Government's theory was based on two propositions. First, the Government charged that the

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Procedure "involves many steps, including selective culture and expansion of a multitude of different types of blood forming and rare bone marrow stromal cells using plastic flasks, additives and nutrients, and environmental conditions…" (DE 1:¶29; JA 17). And second, in two preamble statements which it cited in its Complaint, the FDA stated that it did not consider culture expansion to constitute minimal manipulation. (DE 1:¶28; JA 16-17).

FDA never actually tested the cells used in the Procedure to determine if they were more-than-minimally manipulated; see, e.g. (DE 19-3:¶2; JA 978) (Bauer Declaration, at ¶2); (DE 26-7:¶52; JA 472) (Centeno Affidavit, at ¶52).

III. THE PROCEDURE

To treat their patients using the Procedure, doctor and patient must meet on at least three occasions. During the first patient visit, doctor must assess whether patient is a viable candidate for the procedure. (DE 26-7:¶¶9-11; JA 446-448). As stated by Dr. Centeno in the case below, "[a]pproximately one-fourth of the patients we evaluate are good candidates, about one-half are fair, and about one-fourth are poor candidates." (DE 26-7:¶10; JA 446-447).

After determining that the patient is a viable candidate for the procedure and consulting with the patient regarding risks and benefits, the patient must visit the doctor for treatment. During a second visit, Dr. Centeno or Dr. Schultz take a small

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bone marrow sample from the patient's hip and a sample of blood from the patient's arm. (DE 26-7:¶13; JA 448).

Next, the marrow and blood samples are taken to the Regenerative laboratory. In the laboratory, the marrow sample is centrifuged and separated out into various fractions. (DE 26-7:¶14; JA 448). The marrow-derived cells are then combined with the patient's own blood platelets and a commonly used nutrient solution in a medical grade plastic flask and incubated. (DE 26-7:¶16; JA 449). Over the next several days, the Mesenchymal Stem Cells (MSCs) which adhere to the plastic flask are placed into new flasks with new platelets from the patient's blood sample and new nutrients. (DE 26-7:¶¶18-21; JA 450-451). While in the laboratory, this process is repeated several times to "grow," or multiply, the cells. (DE 26-7:¶21; JA 451). This procedure mirrors that which is used in in-vitro fertilization procedures and is commonly considered to be the practice of medicine. (DE 26-7:¶21; JA 451).[5]

After approximately two weeks, a sample of the expanded cells are sent to the University of Colorado affiliated Colorado Genetics Laboratory for quality testing. *See* (DE 47:2; Addendum 1; JA 925) (Memorandum Opinion, at 2; (*citing* DE 16:¶¶5-10; JA 32) (Amended Answer at ¶¶5-10)). Throughout the time that the

[5] As Dr. Centeno testified below, "every patient's tissue sample is under the direct control of Dr. Centeno or Dr. Schultz. All medications, supplies, or devices used by our clinic to perform the procedure are supported by an applicable drug approval, 510(k) or 510(k) exemption." (DE 26-7: ¶21; JA 451).

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cell sample is being tested, the remainder of the cells are cryopreserved at the Regenerative laboratory. Once the cell sample has passed quality testing, the Regenerative laboratory removes the patient's cells from cryopreservation, combines them with doxycycline and other additives, and places them into syringes.[6] The syringes are placed in sterile bags, brought to the Clinic, and then administered. (DE 47:4; Addendum 1; JA 924) (Memorandum Opinion, at 4; *citing* Compl. ¶11; Answer, ¶¶11,13). Finally, "[t]he stem cells…begin to repair the patient's degenerated or injured area. The repair process usually takes between 3-6 months but many patients demonstrate marked improvement within 1-3 months." (DE 47:4; JA 924)*; see also*, (DE 26-7:¶¶22-33) (detailing Regenerative's release criteria and safety protocols).

The Procedure has been examined by the Colorado Board of Medicine and has been determined to be a medical procedure fully compliant with Colorado law; *see*, Affidavit of Gus R. Michaels III, Esq., (DE 26-19: #12; JA 817); *see also* (DE 26:6).

[6] As testified by Dr. Centeno, doxycycline is used in the Procedure "to prevent the bacterial contamination of...tissue in culture. Doxycycline is a commonly used antibiotic for multiple purposes." (DE 26-8:¶114(c); JA 505i).

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SUMMARY OF ARGUMENT

[D]eference is not abdication. This case illustrates the significance of that distinction.

Otay Mesa Property L.P. v. DOI, 646 F.3d 914, 916 (D.C. Cir. 2011).

This case is about the Federal Government's efforts to regulate the practice of medicine by restricting the use of an *autologous* stem cell procedure – i.e. a procedure performed by a medical doctor involving the use of a patient's own cells to treat that same patient's injuries.

Although it described the case below as a "close" one, the District Court granted summary judgment to the Government without even mentioning four of the Appellants' five affidavits or any of Appellants' affirmative defenses. By doing so and ignoring genuine issues of material fact, the District Court improperly weighed the evidence before it in violation of Fed.R.Civ.P. 56.

Next, the District Court ruled that the Procedure constituted the manufacturing of a biological drug as opposed to the practice of medicine without citing the Colorado law defining the practice of medicine or discussing how it might apply to the Procedure. The District Court's disposition was thus severely incomplete, especially to the extent that it failed to consider whether the statutory scheme was coherent and consistent, and likewise failed to consider any of this Court's or the Supreme Court's relevant jurisprudence.

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Additionally, the District Court ruled that the Procedure constituted the more-than-minimal manipulation of stem cells without mentioning any of the evidence submitted by the Appellants on that issue, and "deferred" to the Government's interpretation of that term without offering any explanation as to why and refusing to allow the Appellants to challenge the lawfulness of the Government's position. This ruling again violated Rule 56, and improperly deferred to FDA rules promulgated in violation of the APA.

Next, in ruling that the Procedure triggered the Commerce Clause, the District Court relied on inapposite, outdated decisions from other circuits and failed to even cite the last seventeen years of Supreme Court jurisprudence governing the issue. The District Court's ruling on this issue calls for the complete regulation of the practice of medicine by the FDA and should be overturned.

Moreover, even though it was directly on point with this case, the District Court made no mention of *United States v. Evers*, 643 F.2d 1043 (5th Cir. 1981) in its discussion of the Government's misbranding claim. Given that *Evers* was directly on point, the District Court's ruling here was erroneous.

The District Court's dismissal of the Appellants' Counterclaims was no less terse and no less erroneous. First, even though the Government specifically used a preamble statement as the foundation upon which to make its more-than-minimal manipulation case, the District Court held that the preamble statement was not only

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non-final, but that the FDA's own regulations create a categorical bar to judicial review of FDA preamble statements. The District Court similarly failed to discuss any of this Court's jurisprudence governing the issue of whether the preamble statement was actually a legislative rule promulgated in violation of the APA.

Next, the District Court dismissed the Appellants' Counterclaim attacking the jurisdictional basis of the Part 1271 regulations by stripping critical language away from the Counterclaim, ruling on the issue based solely on the contents of a regulatory preamble, and misquoting the statute which gave the FDA the authority to write regulations in the first place.

Finally, the District Court entered a lengthy and detailed Permanent Injunction against the Appellants, which was identical to the draft provided by the Government to the District Court as an attachment to its Motion for Summary Judgment. In signing the Order, the District Court made no findings regarding why the individual terms were appropriate, or why the Appellants should have been enjoined at all.

All of this was erroneous and should be reversed on appeal.

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ARGUMENT

I. THE DISTRICT COURT ERRONEOUSLY ENTERED SUMMARY JUDGMENT IN FAVOR OF THE GOVERNMENT.

A. Standard of Review

This Court reviews the District Court's grant of summary judgment *de novo*. *Otay Mesa Property, L.P.* v. *Department of Interior*, 646 F.3d 914, 916 (D.C. Cir. 2011); *citing Hendricks v. Geithner*, 568 F.3d 1008, 1011 (D.C. Cir. 2009).

In reviewing the District Court's grant of summary judgment, this Court applies the same standard as the District Court: "summary judgment may be granted only where 'there is no genuine issue as to any material fact and…the moving party is entitled to a judgment as a matter of law.'" *McCready v. Nicholson*, 465 F.3d 1, 7 (D.C. Cir. 2006); *quoting Maydak v. United States*, 363 F.3d 512, 515 (D.C. Cir. 2004); *citing* Fed.R.Civ.P. 56(c); *see also, Tao v. Freeh*, 27 F.3d 635, 638 (D.C. Cir. 1994).

At the summary judgment stage, "the judge's function is not…to weigh the evidence and determine the truth of the matter but to determine whether there is a genuine issue for trial." *Anderson v. Liberty Lobby*, 477 U.S. 242, 249 (1986). As this Court has stated, "a dispute over a material fact is 'genuine' if the evidence is 'such that a reasonable jury could return a verdict for the nonmoving party.'" *McCready*, 465 F.3d at 7; *quoting George v. Leavitt*, 407 F.3d 405, 410 (D.C. Cir.

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2005). Furthermore, at summary judgment, "all inferences must be viewed in a light most favorable to the non-moving party." *Id., quoting Tao,* 27 F.3d at 638.

B. The District Court Erred by Ruling that the Procedure was a Drug.

At issue in the case below was whether the Procedure constituted the manufacturing of a drug as regulated and defined by Federal law or the practice of medicine as regulated and defined by Colorado law. In resolving that the Procedure was a drug, the District Court looked no further than the federal definition of drugs; 21 U.S.C. § 321(g)(1)(B)&(C). This appears to have been a "'Chevron One' disposition." *ABA v. FTC*, 430 F.3d 457, 478 (D.C. Cir. 2005); *citing Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837, 842-843 (1984).

However, the District Court's analysis was facially incomplete. To be sure, the District Court relied on *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 450 (2002) to support the proposition that "in all statutory construction cases, ***we begin with*** the language of the statute." *Id.*; (DE 47:9; Addendum 1; JA 932) (Memorandum Opinion, at 9); (emphasis added). Relying on ***only*** that language, the District Court ruled that "the cell product used in the…Procedure meets the statutory definition for…a 'drug' under the FFDCA...."

But the District Court ignored critical language from *Barnhart*. In *Barnhart*, not only did the Court hold that "***we begin with*** the language of the statute," the Court also held that "the inquiry ceases ***if the statutory language is unambiguous***

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and the statutory scheme is coherent and consistent." *Id.* (internal quotations omitted) (emphasis added). In other words, as the jurisprudence of this Court makes clear, courts are instructed to "employ 'the traditional tools of statutory construction,'" *Shays v. FEC*, 414 F.3d 76, 84 (D.C. Cir. 2005); *quoting*, *Chevron*, 467 U.S. at 842-43, n.9, including examining "the statute's text, legislative history, and structure[,] as well as its purpose," *Id*, *quoting Bell Atl. Tel. Cos. v. FCC*, 131 F.3d 1044, 1047 (D.C. Cir. 1997) (citations omitted). As the Supreme Court set forth in *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000),

> In determining whether Congress has specifically addressed the question at issue, a reviewing court should not confine itself to examining a particular statutory provision in isolation. The meaning – or ambiguity – of certain words or phrases may only become evident when placed in context. It is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme. A court must therefore interpret the statute as a symmetrical and coherent regulatory scheme, and fit, if possible, all parts into a harmonious whole. Similarly, the meaning of one statute may be affected by other Acts, particularly where Congress has spoken subsequently and more specifically to the topic at hand. In addition, we must be guided to a degree by common sense as to the manner in which Congress is likely to delegate a policy decision of such economic and political magnitude to an administrative agency.

Id.; (internal citations and quotations omitted.)

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In this case, the statutory language is not so unambiguous, nor the statutory scheme so coherent or consistent, to allow the Court to define the Procedure a drug without acknowledging the State of Colorado's role in regulating and defining the practice of medicine within its borders; *Barnhart*, 534 U.S. at 450. To be sure, it is well settled that Congress has left the practice of medicine to the States to regulate; *see e.g. Betancur v. Florida Dep't of Health*, 296 Fed. Appx. 761, 763 (11th Cir. 2008), "[s]tates retain the police power to regulate professions, such as the practice of medicine." *citing Watson v. State of Maryland*, 218 U.S. 173, 176 (1910); *see also Linder v. United States*, 268 U.S. 5, 18 (1925). As stated by the Court in *Chaney v. Heckler*, 718 F.2d 1174, 1180 (D.C. Cir. 1984),[7] "Congress exempted the practice of medicine from the Act so as not to limit a physician's ability to treat his patients."[8]

This well settled principle raises two critical issues with respect to the reach of 21 U.S.C § 321(g)(1)(B)&(C) and whether the District Court properly relied upon it as its ***sole*** basis for determining that the Procedure was a drug. ***First***, if the FDCA was not designed to ***regulate*** the practice of medicine, how could the

[7] *Overruled on other grounds as stated in Heckler v. Chaney*, 470 U.S. 821 (1985).

[8] The FDA has itself recognized this principle: "Throughout the debate leading to enactment [of the Act], there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient." *Id.*, at n.16; *quoting* 37 Fed.Reg. at 16503.

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District Court rely exclusively upon the FDCA to ***define*** the practice of medicine? ***And second***, if the States were left the power to regulate the practice of medicine, how could the District Court have determined that the Procedure was not the practice of medicine without discussing or even citing Colorado law?

Colorado's definition of "practice of medicine" clearly includes the Procedure. That law, which is found at C.R.S. § 12-36-106(1), defines the "practice of medicine" as follows:

> (1) For the purpose of this article, "practice of medicine" means:
>
> (a) Holding out one's self to the public within this state as being able to diagnose, treat, prescribe for, palliate, or prevent any human disease, ailment, pain, injury, deformity, or physical or mental condition, whether by the use of drugs, surgery, manipulation, electricity, telemedicine, the interpretation of tests, including primary diagnosis of pathology specimens, images, or photographs, or any physical, mechanical, or other means whatsoever;
>
> (b) Suggesting, recommending, prescribing, or administering any form of treatment, operation, or healing for the intended palliation, relief, or cure of any physical or mental disease, ailment, injury, condition, or defect of any person with the intention of receiving therefor, either directly or indirectly, any fee, gift, or compensation whatsoever;
> …
> (e) Performing any kind of surgical operation upon a human being;

Id.; *see* (DE 16: Counterclaims ¶¶12,50; JA 43, 51).

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Had the District Court referenced Colorado's definition of "practice of medicine," it could not have ignored the overlap of State and Federal law present in this case. On the one hand, the District Court ruled that the Procedure was a drug because it was designed to mitigate and treat injury and therefore came within the reach of 21 U.S.C § 321(g)(1)(B)(&(C). However, on the other hand, the District Court never discussed the issue of whether the Procedure constituted a "surgical operation" or a "form of treatment, operation, or healing" which would bring it within the scope of C.R.S. § 12-36-106(1). The District Court's failure to fully analyze this complex issue rendered its decision severely incomplete, especially to the extent that it never considered whether the statutory scheme was "coherent and consistent." *Barnhart*, 534 U.S. at 450.[9]

In reality, the FDCA is silent as it relates to autologous stem cell procedures.[10] While this silence *may* be viewed as an ambiguity, "the existence of ambiguity is not enough per se to warrant deference…" *ABA v. FTC*, 430 F.3d 457,

[9] The District Court also wrote that the Appellants' intended use of the procedure – i.e. to treat injuries – was determinative of the issue of whether the Procedure was a drug; (DE 47:11-12; JA 934-935). Based on that reasoning, ***all*** medical procedures could fall within that definition and thus be regulated as drugs. We doubt that Congress intended such a result without even muffled hints. Congress "does not, one might say, hide elephants in mouseholes." *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 468 (2001).

[10] We note that there "is no similar example in the history of medicine where a bodily tissue or cell was taken from a patient, manipulated in some fashion, and therapeutically applied *only to that same patient*, in which the process was considered the manufacture of a drug." (DE 26-2:1; JA 131) (Freeman Affidavit at 1).

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469 (D.C. Cir. 2005). Instead, this Court has held that the "ambiguity must be such as to make it appear that Congress either explicitly or implicitly delegated authority to cure that ambiguity." *Id.* Moreover, "[t]he deference mandated in *Chevron* 'comes into play, of course, only as a consequence of statutory ambiguity, and then *only* if the reviewing court finds an implicit delegation of authority to the agency." *Id., quoting Sea Land Serv. Inc. v. Dep't of Transp.*, 137 F.3d 640, 645 (D.C. Cir. 1998) (emphasis in original).

So, recognizing that a) Congress has specifically left the regulation (and definition) of the practice of medicine to the states, b) Colorado law clearly defines the Procedure as the practice of medicine, and c) the FDCA is silent regarding autologous stem cell procedures, the District Court should have ruled that the Procedure was not a drug at Chevron Step One; *see ABA v. FTC*; *Gonzalez v. Oregon*; *FDA v. Brown & Williamson*.

Although we relied extensively upon several cases from this Court and the Supreme Court addressing how courts must proceed when confronting the overlapping of State and Federal law, the District Court cited none of them. These cases are highly instructive here, as they show that merely because a definitional statute is semantically broad enough to ensnare a practice that a Federal agency wishes to regulate, it does not necessarily follow that the agency has the authority to engage in such regulation; *see Gonzalez v. Oregon*, 546 U.S. 243 (2005)

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(refusing to defer to Attorney General's ruling that state-sanctioned physician assisted suicide was not "legitimate medical purpose"); *FDA v. Brown & Williamson Tobacco Corp*, 529 U.S. 120, 160-61 (2000) (striking down FDA regulation defining cigarettes as "drug delivery devices" to be regulated as medical devices); *ABA v. FTC*, 430 F.3d at 467-468 (setting aside FTC's determination that lawyers were "financial institutions" as defined by the Gramm Leach Bliley Act.)

In the case below, the District Court studied in isolation the federal statute defining drug and ruled that it was broad enough to define the Procedure. Based on that ruling alone, and without citing State law or any case governing how conflicts between State and Federal law must be decided, the District Court entered a "Chevron One" disposition that the Procedure was a drug ***and not*** the practice of medicine. The District Court's holding should be reversed, and this Court should hold that the Procedure does not constitute the manufacturing of a drug. [11]

[11] For the same reasons set forth above, the District Court's decision could also be reversed at Chevron Step Two; *see e.g. ABA v. FTC*, 430 F.3d at 471 ("All the reasons set forth above for our determination that Congress did not intend to leave sufficient ambiguity to support deferential review return to convince us that he interpretation is not reasonable even if we afford it deference.")

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C. The District Court Erred in Ruling that the Procedure Involved "More-than-Minimal" Manipulation and was therefore a "351 HCT/P."

The other primary issue in the case below was whether the Procedure was a biological product, and if so, how it would be regulated under the PHSA.

In its Complaint, the Government charged that because the Procedure involved the more-than-minimal manipulation of stem cells and failed the test set forth at 21 C.F.R. § 1271.10, the Appellants could not treat their patients using the Procedure without an approved biologics license application. The District Court, for reasons we describe below as error, endorsed in full the Government's position.

1. The District Court erred in ruling that no genuine issue of material fact existed with respect to the Government's "more than minimal manipulation" claim.

In the case below, the Appellants aggressively denied the Government's "more-than-minimal manipulation" allegations. First, the Appellants denied in their Answer that they "more-than-minimally manipulated" or "changed the relevant biologic characteristics" of anything, DE 16, and provided ample testimonial support to the District Court, including the following:

> Centeno Affidavit, (DE 26-7:¶¶26-33; JA 453-458) (describing Procedure's safety protocols); (DE: 26-7:¶¶45-57; JA 469-477) (criticizing FDA's position on "minimal manipulation" issue, and concluding that the Procedure involves "no more manipulation of cells than that which occurs in the body itself or with other medical culture procedures that are not regulated as drugs.")

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Henderson Affidavit, (DE 26-20; JA 819-829) (comparing the Procedure to in-vitro fertilization (IVF), concluding that neither IVF nor the Procedure "is similar to the mass manufacture of stem cells in bioreactors for mass manufacture and distribution.")

Angle Affidavit,(DE 26-21:¶14: JA 836) (comparing the Procedure to in-vitro fertilization, describing the Procedure to be safer and more sterile); (DE 26-21:¶32; JA 844) ("Nothing is being removed from the culture media and subsequently isolated and purified for subsequent patients. Cells are not being treated in an effort to change their makeup or create given adult-type cells. Cells are not being homogenized, lysed or treated in some way to extract anything from them that can then be purified and concentrated for use in other humans."); (DE 26-21:¶36; JA 845) ("The cells have divided, but there has been nothing done to them to transform them, nothing done to cause them to secrete anything, nothing done to bring about any change in them that would not or could not have happened in the body…In RS's case the cells are being cultured for a few days in an environment that allows them to replicate, but they are not being manipulated for multiple tissue-engineered construct production…")

Freeman Affidavit, (DE 26-2:¶¶8(g)-(h); JA 136-137) (comparing the Procedure to in-vitro fertilization and platelet based wound care, both of which involve the use of autologous cells which have been cultured *ex vivo*, but neither of which are regulated as drugs or biological products).

See also, (DE 26:64 ¶¶9-10; JA 100-101) (Appellants' "Statement of Material Facts Genuinely in Dispute," at Part II, ¶¶9-10).

The District Court did not address any of this testimony and decided the "close question" below in favor of the Government. It is clear that there existed a number of genuine issues of material fact regarding whether the Procedure involved the "more-than-minimal manipulation" of stem cells which mandated the denial of the Government's motion for summary judgment.

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2. The District Court erred in "deferring" to the Government with respect to the Government's "more-than-minimal manipulation" allegation.

Rather than evaluating the Government's Motion for Summary Judgment consistent with Rule 56 and this Court's controlling case law, the District Court "deferred" to the Government and closed the issue without addressing the factual issues in dispute; (DE 47:13-14; Addendum 1; JA 936-937) (Memorandum Opinion, at 13-14). In short, the District Court held that "the FDA's conclusion that the…Procedure does not meet the regulatory definition of 'minimal manipulation' is entitled to substantial deference" without regard to any disputed issues of fact or law. (DE 47:13; Addendum 1; JA 936) (Memorandum Opinion, at 13; (internal citations omitted)). The District Court thus found that the Procedure constituted the more-than-minimal manipulation of HCT/Ps based upon nothing more than the naked claims of the Government. This ruling was erroneous.

First, merely because the Procedure involved "many steps," it does not necessarily follow that the Procedure involved more-than-minimal manipulation, and it certainly does not mean that the Government is entitled to deference. For starters, the Government's "many steps" proposition was never asserted prior to the filing of its suit against the Appellants and appears nowhere in the administrative record of the regulations. This position was nothing more than a "convenient litigating position" or "post hoc rationalization" of an

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incomprehensible regulation and should thus have received no deference; *see Bowen v. Georgetown University Hospital*, 488 U.S. 204, 212-13 (1988).

The District Court also erred when it blindly deferred to the Government's "many steps" proposition because, as revealed by the administrative record, the FDA took a diametrically opposed position when the regulations at issue were being promulgated; see (PA 000267)[12] (where FDA explains that the "intent" of the regulations is to "look at cells based on function, not so much as how much processing is done to them." In other words, "if [the HCT/P's] function is not otherwise changed," processing "would probably not per se count as more than minimal manipulation."); *see INS v. Cardoza-Fonseca*, 480 U.S. 421, 446, n.30 (1987) ("An agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is entitled to considerably less deference than a consistently held agency view.") (internal citations omitted). The FDA never explained its change in position and the Court did not explain why this new, *post hoc* interpretation was entitled to deference.

Further, the preamble statements relied upon by the Government for the proposition that expansion *per se* constitutes more-than-minimal manipulation

[12] In the case below, the Government produced an administrative record of approximately 10,000 pages, each of which had a specific prefix. The "PA" prefix used here designates the record of FDA's March 17, 1997 public hearing regarding its "Proposed Approach to Regulation of Cellular and Tissue Based Products" dated February 28, 1997. 62 Fed. Reg. 9721.

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were also unworthy of deference. These preamble statements, which the Government argues to be both determinative ***and*** non-final, were not subject to notice and comment rulemaking procedures and were thus promulgated in contravention of the APA. As the Supreme Court stated in *Wyeth v. Levine*, 555 U.S. 555, 577 (2009), the FDA's views here should be perceived as "inherently suspect."

For all of these reasons, the District Court erred in deferring to the Government on the question of whether the Procedure constituted the more-than-minimal manipulation of cells.

D. The District Court Erred in Ruling that the Procedure did not Constitute the Practice of Medicine.

The Appellants' contended below that because the Procedure constituted the practice of medicine as defined by Colorado law, the Procedure was not subject to the jurisdiction of the FDA. The Appellants also argued that the FDA's 1271 regulations, which purport to give the FDA the jurisdiction to regulate the practice of medicine, are *ultra vires* and arbitrary and capricious.

In its papers, the Government argued that because the Procedure was a drug which had not been approved by FDA, the "practice of medicine" did not afford the Appellants a "safe harbor." (DE 19:35) (Motion for Summary Judgment at 35). According to the Government, the Appellants' "practice of medicine" defenses were invalid because the only definition of that term ever endorsed by the FDA or

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any federal court was "a physician prescribing ***lawfully marketed products*** for uses other than those for which they are approved, licensed, or cleared by FDA."(DE 20:18) (Motion to Dismiss at 18).[13] Although the District Court did not explain its reasoning in its Memorandum Opinion, it appears to have ignored Colorado's definition of that term and agreed entirely with the FDA's position; *see* (DE 47:18-19; Addendum 1; JA 941-942) (Memorandum Opinion, at 18-19).

For a variety of reasons – all of which the Appellants briefed below, but none of which were mentioned by the District Court – the District Court erred in ruling that the Procedure did not constitute the practice of medicine. We outline those reasons below:

1. The District Court erred in ruling as a matter of fact that the Procedure did not constitute the practice of medicine.

First, the District Court improperly weighed the evidence before it when answering this "close question." To be sure, the Appellants submitted to the District Court five affiants, two of whom are medical doctors and two of whom are PhDs who testified to facts that establish that the Procedure was the practice of medicine as opposed to the manufacturing of a drug or biologic product; *see e.g.*

> Freeman Affidavit, (DE 26-2:¶9; JA 143-144) (concluding that the Procedure "is not a drug manufacturing process, and does not fit any previously known definition of drug manufacture…By any and all

[13] As described by *amicus curiae* Association of American Physicians and Surgeons Inc., the Government's definition here echoed Louis XV: "*avant moi, l'abysse*" or "before me, there was nothing." (DE 35-8).

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> reasonable definitions, [the Procedure] is a *medical* procedure, and one that can only be delivered by the hands of a licensed and appropriately trained clinician.");
>
> Centeno Affidavit, (DE 26-7:¶6; JA 444-445) (describing Colorado Medical Board audit of Procedure and conclusion that the Procedure constituted the practice of medicine); (DE 26-7: ¶¶8-9; ¶¶34-37; JA 445-446; 458-464) (and Appendices F, G, H) (describing medical community's reaction to FDA's regulation of autologous stem cell procedures);
>
> Henderson Affidavit, (DE 26-20:¶4; JA 820) (describing the Procedure as the practice of medicine "and in no way similar to the drug mass manufacturing process.");
>
> Angle Affidavit, (DE 26-21:¶17; JA 838) ("I cannot conceive of how this can be anything other than the practice of medicine.")

The District Court did not acknowledge any of this testimony.

Additionally, the Appellants submitted *The Belmont Report* to the District Court to be used in evaluating as a matter of fact whether the Procedure constituted the Practice of Medicine; *see* (DE 26:11-14).[14] The Belmont Report was relevant to the Government's Motion for Summary Judgment for two interrelated reasons. First, as we advised the District Court, *The Belmont Report* could have assisted in the evaluation as an issue of fact whether the Procedure constitutes the practice of medicine. As described by Dr. Centeno, he developed the Procedure consistent with the terms of the Belmont Report; (DE 26-7, 8: ¶¶67-71; JA 480-483)

[14] A copy of *The Belmont Report* is attached hereto as Addendum 9. This document, as well as many of its companion reports, was attached to the Appellants' Opposition to the Government's summary judgment motion but was never addressed by the District Court.

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(Centeno Affidavit). The Belmont Report could have thus also assisted the District Court in understanding whether the Procedure was the practice of medicine or something else entirely.[15]

By not even mentioning it in its Memorandum Opinion, the District Court improperly weighed Appellants' evidence against that of the Government. This weighing exercise, which substituted for the search for a triable issue of fact mandated by Rule 56, was error and requires reversal.[16]

2. The District Court erred in "deferring" to the Government's definition of the practice of medicine.

The District Court also appears to have given deference to the FDA regarding what constitutes the practice of medicine where none was due. Again, it is well settled that the regulation of the practice of medicine has been left to the individual states as opposed to the FDA. As stated by the Court in *Gonzalez v. Oregon*, "[d]eference in accordance with *Chevron*…is warranted only 'when it appears that Congress delegated authority to the agency generally to make rules

[15] As we explain below in Part III of our Argument, *The Belmont Report* was also relevant to the Government's request for a permanent injunction which was based, at least in part, on the Government's theory that the Appellants were experimenting on their patients.

[16] It is well settled in this Circuit that "decision by summary judgment is disfavored when additional development of facts might illuminate the issues of law requiring decision." *Nixon v. Freeman*, 670 F.2d 346, 362 (D.C. Cir. 1982). However, even though it granted the Government's summary judgment motion prior to the start of discovery, the District Court never explained why it was departing from that principle.

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carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority.'" 546 U.S. at 255; *quoting*, *United States v. Mead Corp.*, 533 U.S. 218, 226-227 (2001); *see also American Library Assoc. v. FCC*, 406 F.3d 680, 698-699 (D.C. Cir. 2005). Otherwise, the interpretation is "entitled to respect" only to the extent it has the "power to persuade." *Id., quoting Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944).[17] The FDA's definition of the practice of medicine is entitled no deference because the FDA was never delegated authority to write it in the first place.

Moreover, the Government's definition of practice of medicine was not entitled to deference because it violated the "presumption against pre-emption." *Gonzales v. Oregon*, 546 U.S. at 274; *citing Rush Prudential HMO, Inc. v. Moran*, 536 U.S. 355, 387 (2002). As stated by the Court in *Medtronic v. Lohr*, 518 U.S. 470, 485 (1996):

> [B]ecause the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action. In all pre-emption cases, and particularly in those in which Congress has "legislated...in a field which the States have traditionally occupied," we "start with the assumption that the historic police powers of the States were not superseded by the Federal Act unless that was the clear and manifest purpose of Congress."

[17] In our Opposition to the Government's Motion to Dismiss, we describe this "initial or prequel" examination of the deference issue as "Chevron Step Zero." DE 25, at 12-13; *see also*, Jacob E. Gersen, *Overlapping and Underlapping Jurisdiction in Administrative Law*, 2006 Sup. Ct. Rev. 201, 16 (2007).

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Id.; (internal citations omitted). Thus, because the Government's definition of the practice of medicine displaces Colorado's definition of that term, and because it does so without so much as "muffled hints" from Congress authorizing it, the definition was *ultra vires* and not entitled deference:

> Just as the conventions of expression indicate that Congress is unlikely to alter a statute's obvious scope and division of authority through muffled hints, the background principles of our federal system also belie the notion that Congress would use such an obscure grant of authority to regulate areas traditionally supervised by the States' police power.

Gonzales v. Oregon, 546 U.S. at 272.

The definition of "practice of medicine" urged by the Government below (and apparently endorsed by the District Court) should also have received no deference because it was fundamentally different than the position the Government had previously taken on the same issue. Without belaboring anew the fact that the FDA lacks the jurisdiction to define the "practice of medicine" in the first place, it should be noted that the Government previously called for a far broader definition of the practice of medicine, and did so before the United States Supreme Court in *Gonzales v. Oregon*.

In support of its position in *Gonzales v. Oregon* – i.e. that physician assisted suicide was not a "legitimate medical purpose" – the Government wrote as follows:

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> [T]he operative requirements for a "prescription" to be valid under the CSA are that it be issued for a "legitimate medical purpose" and "in the usual course of professional treatment." 21 C.F.R. 1306.04(a). *See* 21 U.S.C. 830(b)(3)(A)(ii). Because the CSA and implementing regulations do not specifically define those terms, they should be given their "ordinary meaning." *See, e.g.*, *Asgrow Seed Co. v. Winterboer*, 513 U.S. 179, 187 (1995); *FDIC v. Meyer*, 510 U.S. 471, 476 (1994). The ordinary meaning of the term "medical" is "pertaining or related to the healing art or…to 'medicine,'" 9 Oxford English Dictionary 546 (2d ed. 1989), and the term "medicine" refers to "that department of knowledge and practice which is concerned with the cure, alleviation, and prevention of disease in human beings, and with the restoration and preservation of health," *id. at 549;* see Webster's Third New International Dictionary 1402 (1966) ("the science and art dealing with the maintenance of health and the prevention, alleviation, or cure of disease"); The Random House Dictionary of the English Language 1194 (2d ed. 1987) ("the art or science of restoring or preserving health or due physical condition").

Brief for the Petitioners, *Gonzales v. Oregon*, 546 U.S. 243 (2006), available at 2005 U.S. S.Ct. Briefs LEXIS 354, 40-42. The conflict between the Government's two definitions is obvious. In this case, the Government argued that the definition of the practice of medicine should be limited to the off-label use of drugs, but in *Gonzales v. Oregon* the Government argued for a definition that was *at least* as broad as the Colorado statute which the Government and District Court alike cast aside as superfluous. Accordingly, the Government's position in the case below was

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ultra vires, inconsistent with its prior interpretation of that same term, and entitled to no deference; *see Cardoza-Fonseca*, 480 U.S. at 446, n.30.

E. The District Court Erred in Ruling that the Appellants Violated 21 U.S.C. § 331(k).

The District Court ruled that the Appellants violated 21 U.S.C. § 331(k) in two ways. First, the District Court wrote that the Appellants adulterated the drug they manufactured; Memorandum Opinion, at pp.15-16. Second, the District Court wrote that the Appellants misbranded the drug they manufactured; (DE 47:16-17; Addendum 1; JA 939-940) (Memorandum Opinion, at 16-17). According to the District Court, both violations occurred because the "cell product" was "(1) held for sale and prior to such sale had been (2) ship[ped] in interstate commerce." (DE 47:14; Addendum 1; JA 937) (Memorandum Opinion, at 14; *citing* 21 U.S.C. § 331(k)). All of these holdings are erroneous and should be reversed.

1. The District Court erred in holding that the Procedure was "subject to the Commerce Clause."

Pursuant to its Commerce Clause authority, Congress enacted 21 U.S.C. § 331(k), which renders unlawful:

> [t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

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§ 331(k) is part of the FDCA, which "rests upon the constitutional power resident in Congress to regulate interstate commerce. To the end that the public health and safety might be advanced, it seeks to keep interstate channels free from deleterious, adulterated and misbranded articles of the specified types. It is in that interstate setting that the various sections of the act must be viewed." *United States v. Walsh*, 331 U.S. 432, 434 (1997); *citing United States v. Dotterweich*, 320 U.S. 277, 280 (1943).

In its Motion for Summary Judgment, at p.23, the Government framed the issue as whether the "Defendants' Cultured Cell Product is held for sale after shipment of one or more of its components in interstate commerce." (DE 19:23). In other words, the "FDA attempts to regulate the individual medical treatment of patients by licensed physicians in their own states based solely on the use of an unadulterated drug, doxycycline…,that at one time crossed state lines in the *intrastate* treatment of Regenerative patients." (DE 37:3) (Brief of *Amicus Curiae* American Association of Orthopaedic Medicine, at 3).

The Government's framing of this issue was derived from *United States v. Dianovin Pharmaceuticals*, 475 F.2d 100 (1st Cir. 1973) and *Baker v. United States*, 932 F.2d 813 (9th Cir. 1991). Although *Baker* and *Dianovin* are inapposite and should not have governed the case below, the District Court relied upon them

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as its ***sole*** basis for ruling that the Procedure was "subject to the Commerce Clause."

In *Dianovin*, the First Circuit ruled that because the ingredients in Dianovin's "vitamin K for injection" product – including the vitamin K itself – were shipped in interstate commerce to Dianovin before being placed into ampules for sale, "such activities fell within § 331(k) and conferred jurisdiction to restrain violations thereof upon the district court." *Dianovin*, 475 F.2d at 103. Similarly, in *Baker*, Baker entered a plea of *nolo contendere* to manufacturing and distributing synthetic heroin exclusively in California. *Baker*, 932 F.2d at 814. On appeal to the Ninth Circuit, Baker attempted to "unravel the factual basis" of his conviction by arguing that the Commerce Clause did not apply to his conduct; *Id.*, at 814. However, the Ninth Circuit held that Baker was estopped from doing so and, in dicta, ruled that § 331(k) was nevertheless violated; *Id.*

In this case, unlike the synthetic heroin in *Baker* or the vitamin K in *Dianovin*, the Procedure involves the use of a patient's own cells to heal the patient's own injuries. The entire process occurs at the Appellants' medical facilities in Broomfield, Colorado. Moreover, unlike manufacturing synthetic heroin or interstate delivery of vitamin K, the Procedure constitutes the practice of medicine as defined by State law and is performed on a patient-by-patient basis by physicians licensed to practice medicine in the State of Colorado. Thus, the

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question of whether the Procedure is "subject to the Commerce Clause" is fundamentally different than the question regarding the manufacture and distribution of synthetic heroin or vitamin K.

First of all, the scope of the Commerce Clause "must be considered in the light of our dual system of government and may not be extended so as to embrace effects upon interstate commerce so indirect and remote that to embrace them, in view of our complex society, would effectually obliterate the distinction between what is national and what is local and create a completely centralized government." *United States v. Lopez*, 514 U.S. 549, 557 (1995); *quoting NLRB v. Jones & Laughlin Steel*, 301 U.S. 1, 37 (1937); *see also Morrison*, 529 U.S. at 618-19 ("we always have rejected readings of the Commerce Clause and the scope of federal power that would permit Congress to exercise a police power.")

Thus, when a doctor purchases an unadulterated item from another state for use in his practice, he does not automatically become a federally regulated entity or somehow become subject to the Government's Commerce Clause jurisdiction; *see e.g. A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495, 546 (1935); *see also Jones v. United States*, 529 U.S. 848 (2000) ("Were we to adopt the Government's expansive interpretation…, hardly a building in the land would fall outside the federal statute's domain. Practically every building in our cities, towns and rural areas is constructed with supplies that have moved in interstate

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commerce, served by utilities that have an interstate connection, financed or insured by enterprises that do business across state lines, or bears some other trace of interstate commerce.")

What the Government's position in this case stands for is actually more than just the elimination of the separation between that which is federal and that which has been reserved to the individual states. To be sure, the Appellants in this case practice medicine, and like all other doctors, purchase *unadulterated* products from other states for use in their practice. Here, however, the Government seeks to employ that routine, innocuous, interstate purchase as the foothold upon which to regulate and define the practice of medicine, ***and*** does so without so much as a muffled hint from Congress authorizing it; *see Jones*, 529 U.S. at 859 (Stevens, J., concurring) ("we have wisely decided that 'unless Congress conveys its purpose clearly, it will not be deemed to have significantly changed the federal-state-balance.'"); *quoting United States v. Bass*, 404 U.S. 336, 349 (1971).[18]

[18] We note that the Government's position on the Commerce Clause issue changed as the litigation proceeded. Again, the Government's initial position was that the Commerce Clause was triggered because certain "adjunctive" drugs used in the procedure travelled to Colorado from other states; *see Amicus Curiae Brief of American Association of Orthopaedic Medicine*, at 15; (DE 37:15). However, after the Appellants and *amicus curiae* challenged the Government's position, the Government argued in its Reply brief that when taken in the aggregate, the Procedure itself, as well as people travelling in interstate commerce to receive it, "could depress the market for out-of-state drugs that are approved by FDA." (DE 32-1:19-20). In our Motion for Leave to file a Surreply Brief, we argued that the Government's new understanding of the Commerce Clause called for a grossly

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Accordingly, the District Court's endorsement of the Government's position regarding the application of the Commerce Clause to the Procedure should be reversed.

2. The District Court erred in ruling that the Appellants committed adulteration violations.

In the case below, the Government argued that the Appellants adulterated their "cultured cell product" because they did not comply with FDA's Current Good Manufacturing Practice ("cGMP") regulations; *see* (DE 1:¶31; JA 18-19) (Complaint at ¶31); (DE 19:25-28) (Motion for Summary Judgment, at pp. 25-28). In the face of a conflicting record before it, the District Court accepted the Government's claims without analysis. This was error.

Whereas cGMPs are applicable to the manufacturing of FDA-regulated drugs and devices, cGMPs are not applicable to medical practices such as hospitals, doctors offices, ambulatory centers and IVF facilities; *see* 21 C.F.R. §§ 210.2, 211.1; 21 U.S.C. § 353a(a). As previously articulated, the Appellants are engaged in the practice of medicine, treat their patients in a one-on-one basis at the Centeno Schultz medical clinic in Broomfield, Colorado, and have robust safety

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impermissible expansion of the concept of "instrumentalities of interstate commerce," and should have been rejected. (DE 41-1:11 n.5; JA 915). Of course, the District Court never acknowledged our Motion for Leave to File a Surreply Brief or the Government's morphed understanding of the Commerce Clause. Nevertheless, should the Government choose to revive its "depression" argument here, this Court should reject it.

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protocols appropriate for the practice of medicine; *see e.g.* Centeno Affidavit, (DE 26-7:¶¶26-33; JA 453-458) (describing Procedure's safety protocols). As such, the FDA's cGMP regulations are not applicable to the Appellants.

These concepts alone created a genuine issue of material fact regarding the Government's adulteration claim, and the Government's Motion for Summary Judgment should have therefore been denied.

3. The District Court erred in ruling that the Appellants committed misbranding violations.

The Government argued below that the Defendants misbranded "their cultured cell product" by failing to include adequate directions for use on its labeling; (DE 19:28-34). More specifically, the Government argued that the "cultured cell product" is a prescription drug, and because its labeling lacked an 'RX Only" symbol, it was misbranded; (DE 19:29). The District Court fully endorsed this position; *see* Memorandum Opinion, at 16-18; (DE 47:16-18; Addendum 1; JA 939-941).

This exact argument, however, was summarily disposed of in *United States v. Evers*, 643 F.2d 1043 (5th Cir. 1981). In that case, a licensed physician was charged with misbranding prescription "chelating drugs" which he administered intravenously into his patients for the off-label treatment of circulatory disorders; *Id.*, at 1044-1045. In response to the Government's charge that Dr. Evers had misbranded the chelating drugs in violation of § 331(k), the Court held as follows:

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> The requirement which the FDA seeks to impose is nonsensical. Since Calcium EDTA is a prescription drug, the misbranding provision under which Dr. Evers was charged requires him to provide adequate information for use by prescribing physicians. However, Dr. Evers was the only physician who used the Calcium EDTA in question. The government's application of the statute may therefore be reduced to the following proposition: Dr. Evers did not provide adequate information to himself. It is doubtful at best that this interpretation was intended by the drafters of the statute.

Id., at 1053.[19]

As in *Evers*, the Government's misbranding charge against the Defendants boiled down to the proposition that the Appellants did not provide adequate information to themselves. Accordingly, there was at least a genuine dispute regarding the Appellants' alleged violation of § 331(k). However, in ruling that there was no genuine issue regarding whether the alleged misbranding violation,

[19] The Government also argued in its motion for summary judgment, at 33-34, that the Defendants "cultured cell product" could only have been misbranded because "even if Defendants tried to draft adequate directions for use…, it would be impossible to do so based on currently available data." (DE 19:33). However, this argument was also disposed of by the Fifth Circuit in *Evers*, and should be likewise disposed of here. In *Evers*, the Court noted that even though "Dr. Evers' claims for his therapy are not generally accepted by the medical profession, and…the FDA has not approved any chelating drug for use in the treatment of circulatory disorders" Dr. Evers could not be held liable for failing to provide adequate information to himself; *Evers,* 643 F.2d at 1045. The District Court never addressed this precise issue in its Memorandum Opinion, and it should not be endorsed by this Court on appeal.

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the District Court completely ignored *Evers* and made no effort to distinguish it.[20] The Government's Motion for Summary Judgment on the misbranding issue should have been denied, and the District Court's decision should be reversed.

4. The District Court erred in ruling that the Appellants committed adulteration and misbranding violations without acknowledging the Appellants' affirmative defenses relevant to those charges.

Appellants' Affirmative Defenses XI and XII argued, based upon 21 U.S.C. § 353a, that because the FDA had previously approved or licensed the use of autologous, culture expanded HCT/Ps in treating musculoskeletal injuries, the Defendants' use of autologous, culture expanded HCT/Ps in treating the musculoskeletal injuries of their patients was not subject to the adulteration and misbranding provisions of the FDCA. (DE 16:9-10; JA 39-40) *see also* (DE 26:35).

The Government did not address these Affirmative Defenses in its Motion for Summary Judgment. Rather, in its Reply brief, for the first time, the Government argued that there were no questions of material fact concerning Appellants' Affirmative Defenses XI and XII because the Appellants did not satisfy 21 U.S.C. § 353a; (DE 39:33-37). However, the Appellants pled that they

[20] We relied extensively on *Evers* when defending against the Government's misbranding charge before the District Court; (DE 26-37-38). Although the District Court actually cited *Evers* in its discussion of the Commerce Clause issue, Memorandum Opinion, at p.14, it made no mention of it in its discussion of the misbranding issue.

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satisfied the statute and submitted affidavits supporting their position. The District Court ignored these genuine issues of material fact.

21 U.S.C. § 353a sets forth a multi-prong standard for compounded drugs. It provides that the adulteration and misbranding provisions of the FDCA do not apply to compounded drugs so long as the compounding is conducted by a licensed physician or pharmacist on a patient-by-patient basis, and the compounded product meets each of the protocols set forth in § 353a(b)(1). The Procedure fully satisfies the statute.

The Procedure satisfies the first prong, § 353a(b)(1)(A), because there is no applicable United States Pharmacopoeia or National Formulary monograph and the active ingredient of the Procedure is a component of an FDA approved drug; § 353a(b)(1)(A)(II); *see* Centeno Affidavit, at ¶145 (DE 26-8:¶145: JA 521) ("…Carticel is in fact, in part, an MSC cell culture process.").

Next, the Government argued that the Procedure does not qualify for the § 353a safe harbor because it is not "manufactured by an establishment that is registered under [21 U.S.C. § 360]…"; *see* § 353a(b)(1)(A)(ii). However, the Government's argument missed the mark because Appellants are physicians "licensed by law to prescribe or administer drugs" and, consequently, the registration requirement is not applicable to them; *see* 21 U.S.C. § 360(g)(2).

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Likewise, the Government argued without any substantive explanation or evidentiary support that the autologous cells used in the Procedure are not accompanied by valid certificates of analysis. However, this argument ignores the fact that, as Dr. Centeno testified, the Defendants employ a robust set of safety protocols to ensure the purity and integrity of the Procedure, and these protocols include a test conducted on each patient's cells by an outside laboratory; *see* Centeno Affidavit, at ¶32(k) (DE 26-7:¶32(k); JA 457). The Federal requirement of a certificate of analysis is thus satisfied.

Based upon these genuine issues of material fact regarding Appellants Affirmative Defenses, coupled with the fact that the Government's motion and the District Court did not even address them, the District Court's granting of the Government's summary judgment motion was erroneous and should be reversed.

II. THE DISTRICT COURT ERRONEOUSLY GRANTED THE GOVERNMENT'S MOTION TO DISMISS THE APPELLANTS' COUNTERCLAIMS.

A. Standard of Review

In the case below, the District Court considered "matters outside the pleadings" in granting the agency's motion to dismiss. "In so doing, it effectively treated the motion as one for summary judgment," and thus this Court's standard of review mirrors the standard of review it employs when reviewing district courts' decisions to grant summary judgment. *Center for Auto Safety and Public Citizen*

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Inc. v. NHTSA, 452 F.3d 798, 805 (D.C. Cir. 2006). This is a *de novo* standard of review; *Otay Mesa Property, L.P.* 646 F.3d at 916.

Furthermore, "[in] a case like the instant one, in which the District Court reviewed an agency action under the APA, we review the administrative action directly, according no particular deference to the judgment of the District Court." *Association of Private Sector Colleges and Universities v. Duncan*, 681 F.3d 427, 440-41 (D.C. Cir. 2012).

B. The District Court erred in dismissing Counterclaims I, II, III, and VII.

The District Court dismissed Counterclaims I, II, III, and VII because they "challenge[d] the FDA's authority to regulate the practice of medicine." (DE 47:19; Addendum 1; JA 942). Therefore, the District Court dismissed them for reasons discussed in the District Court's ruling on the Government's motion for summary judgment.

We will not restate here our argument that the District Court's analysis of the "practice of medicine" issue was erroneous. However, we will advise this Court as to how the FDA went about the process of determining, in the face of very harsh and vocal criticism, that their regulations were not infringing on the practice

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of medicine over which it has no jurisdiction.[21] Indeed, this process was the basis of Counterclaim II.

Regardless of whether the Procedure actually constitutes the practice of medicine, FDA's determination that its regulations did not infringe upon the practice of medicine was nevertheless arbitrary and capricious. In response to numerous public comments received between 1995 and 2001 arguing that the 1271 regulations would infringe upon the practice of medicine, FDA responded as follows:

> Several comments asserted that we are proposing to regulate the practice of medicine, especially with respect to reproductive tissue and hematopoietic stem cells. We disagree with this comment… We are not attempting to govern practitioners' use of HCT/P's, but rather to ensure that HCT/P's that would be used by practitioners in their treatment of patients are in compliance with applicable regulations, including regulations designed to prevent the transmission or spread of communicable disease.

66 Fed.Reg. 5452.

In short, according to the FDA, it regulates all HCT/Ps regardless of how the HCT/Ps will be used and regardless of applicable State law. However, this

[21] Included in the parties' Joint Appendix at pp. 654 – 716 are letters submitted to FDA by Hyman, Phelps & McNamara P.C., the American Society of Clinical Oncology, the American Red Cross, and King & Spalding LLP. All of these letters were submitted by FDA to Appellants as part of the administrative record, Appellants submitted all of them to the District Court (Centeno Affidavit, DE 26-16: Appx.G), and the District Court ignored all of them in its Memorandum Opinion.

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determination was arbitrary and capricious because it failed to even consider that the individual States, and not the FDA, regulate ***and define*** the practice of medicine. As stated by the Court in *Federal Election Commission v. Rose*, 806 F.2d 1081, 1088 (D.C. Cir. 1986), "[a] determination that an agency made a decision without considering a relevant factor leads to condemning the decision as 'arbitrary and capricious.'" *Id., citing Motor Vehicles Manuf's Assoc. v. State Farm*, 463 U.S. 29, 46-57 (1983). Moreover, "when an administrative decision is based on inadequate or improper grounds, a reviewing court may not presume that the administrator would have made the same decision on other, valid grounds." *American Public Transit Assoc. v. Lewis*, 655 F.2d 1272, 1278 (D.C. Cir. 1981); *citing SEC v. Chenery Corp. (II)*, 332 U.S. 194, 196 (1947).[22]

Here, the arbitrary and capricious nature of the FDA's decision is evidenced by the fact that the FDA's decision ran so far afoul of numerous Executive Orders instructing the agency how to proceed when confronted with issues of federalism and the prospect of preemption. Indeed, throughout the time that the FDA was promulgating the Part 1271 regulations, numerous executive orders were in place governing the FDA's conduct; *see* Executive Order 12612 (October 26, 1987); Executive Order 12866 (September 30, 1993); Executive Order 12988 (February 5,

[22] This rule applies with equal force when agencies err in interpreting statutes: "a reviewing court must always determine whether an administrator properly construed the scope of his statutory authority." *Id., citing Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 416 (1971).

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1996); Executive Order 13083 (May 14, 1998); Executive Order 13132 (August 4, 1999).[23] FDA ignored all of them when writing its Part 1271 regulations, and the District Court ignored all of them when ruling below.

Thus, it is not only clear that Congress specifically intended for the regulation of the practice of medicine to be left to the individual States, but that all three branches of the Federal Government have consistently supported that proposition. Moreover, it is also clear that when Federal agencies such as the FDA address issues that have the potential to impact Federalism, they must, at a minimum, consult with the appropriate representatives of the States "to discern the sentiments of the people and to govern accordingly." Executive Order 12612.

As it relates to licensed physicians treating their patients using autologous stem cell therapies, the FDA ***never*** undertook any research regarding how the 1271 regulations would impact the individual States, and its decision that its regulations did not infringe upon the practice of medicine was thus arbitrary and capricious. For all of these reasons, the Government's Motion to Dismiss the Defendants' Counterclaims should have been denied and the District Court's decision should be reversed.

[23] These Executive Orders are attached hereto as Composite Addendum 7.

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C. The District Court erred in dismissing Counterclaims IV, V and VI.

In its Memorandum Opinion, at 19, the District Court noted that Counterclaims IV, V and VI concern the following FDA preamble statement: "We do not agree that the expansion of mesenchymal cells in culture…[is] minimal manipulation." (DE 47:19; Addendum 1; JA 942). Then, with virtually no legal analysis, the District Court entered an Order creating a *per se* rule that no FDA preamble statement is reviewable in court. The District Court's decision on this issue must not stand.

To clarify, the categorical bar which the District Court created for the FDA is based on two ideas. First, the District Court held that because the FDA has a regulation which says that its preamble statements "do not carry the force of law," the FDA preamble statement ***which the Government used in this case as the basis upon which to sue the Appellants*** could not be challenged. (DE 47:19; Addendum 1; JA 942) (Memorandum Opinion, at 19; *citing* 21 C.F.R. § 1085(d)(1)(&(j)). Second, the District Court held that because this Court recently held in an unrelated case that a preamble statement did "not express a final agency action," the preamble statement in this case likewise did not. *Id., citing Am. Petroleum Inst. v. EPA*, Nos. 10-1079, 10-1080, 2012 WL 2894566, at 9 (D.C. Cir. July 17, 2012).

It takes very little digging into this Court's jurisprudence to realize the error in the District Court's decision. First, merely because an agency says that one of its

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preamble statements is not final, that does not make it so; *see e.g. Barrick Goldstrike Mines Inc. v. Browner*, 215 F.3d 45, 48 (D.C. Cir. 2000) (rejecting the proposition that "if an agency labels its action an 'informal guideline' it may thereby escape judicial review under the APA."); *citing Better Gov't Ass'n v. Department of State*, 780 F.2d 86, 93 (D.C. Cir. 1986).

Second, *Am. Petroleum Inst.* does not stand for the categorical bar to judicial review of agency preambles that the District Court's Memorandum Opinion stands for. Indeed, in *Kennecott Utah Copper Corp. v. United States DOI*, 88 F.3d 1191, 1222 (D.C. Cir. 1996), this Court rejected that notion: "At the outset, we cannot agree…that there is a categorical bar to judicial review of a preamble." *Citing, Center for Auto Safety v. Federal Highway Admin*, 956 F.2d 309, 313 (D.C. Cir. 1992). Instead, rather than being an issue of the form upon which the agency announces a position, the issue is one of substance: "The question of reviewability hinges upon whether the preamble has independent legal effect, which in turn is a function of the agency's intention to bind either itself or regulated parties." *Id.*

In this case, FDA actually used the preamble statement as the basis upon which to sue the Appellants, and its intention to use it to bind the Appellants is obvious. Secondarily, as previously explained, given that "minimal manipulation" is only defined by a "change in the relevant biological characteristics," and that "relevant biological characteristics" has no regulatory definition at all, it becomes

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clear that the FDA ***needs*** its preamble statement to give meaning to its otherwise incomprehensible regulation. In other words, but for the preamble statement, nobody – FDA included – would have any idea as to what constituted a "more than minimally manipulated" HCT/P.

Of course, in the case below, not even the Government took the unsupportable position that the District Court took in its Opinion. Instead, the Government argued that the FDA's preamble statement on expansion was not a "legislative rule" and therefore was not subject to notice and comment rulemaking procedures; *see* (DE 20:25-28).

However, the Government's position (which the District Court never addressed) was incorrect. Indeed, in *Catholic Health Initiatives v. Sebelius*, 617 F.3d 490 (D.C. Cir. 2010) this Court held that "[t]o fall within the category of interpretive, the rule must 'derive a proposition from an existing document whose meaning compels or logically justifies the proposition. The substance of the derived proposition must flow fairly from the substance of the existing document.'" *Id.*, at 494; *quoting* Robert A. Anthony, *"Interpretive" Rules, "Legislative" Rules, and "Spurious Rules: Lifting the Smog*, 8 Admin.L.J. Am.U. 1, 6 n.21 (1994). The Court further elaborated:

> [I]f the relevant statute or regulation "consists of vague or vacuous terms – such as 'fair and equitable,' 'just and reasonable,' 'in the public interest,' and the like – the process of announcing propositions that specify

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> applications of those terms is not ordinarily one of interpretation, because those terms in themselves do not supply substance from which the propositions can be derived."

Id., *quoting Lifting the Smog*, 8 Admin.L.Am.U. at 6, n.21; *see also Paralyzed Veterans of America v. D.C. Arena L.P.*, 117 F.3d 579, 588 (D.C. Cir. 1997) ("The distinction between an interpretative and substantive rule more likely turns on how tightly the agency's interpretation is drawn linguistically from the actual language of the statute or rule. ***If the statute or rule to be interpreted is itself very general, using terms like 'equitable' or 'fair,' and the 'interpretation' really provides all the guidance, then the latter will more likely be a substantive regulation.***") (emphasis added)

Here, the terms "minimal manipulation" and "relevant biological characteristics" supply no substance from which the FDA's rule regarding "expansion" can be derived; *see also, United States v. Picciotto*, 875 F.2d 345 (D.C. Cir. 1989). Thus, FDA cannot insulate its substantive rule by labeling it a mere interpretation.[24]

In this appeal, this Court should reverse the District Court's categorical bar to judicial review of FDA preamble statements, and it should similarly reject any

[24] Of course, as *amicus curiae* Association of American Physicians and Surgeons explained in its brief, to the extent that the FDA's preamble statements were merely interpretive "general statements of policy," they should not have received deference; (DE 35:13) (*citing Pacific Gas & Electric Co.*, 506 F.2d 33, 38-39 (D.C. Cir. 1974)).

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argument the Government may make supporting the idea that its preamble statement was merely interpretive or otherwise non-final.

D. The District Court erred in dismissing Counterclaim VIII.

In Counterclaim VIII, the Appellants charged that FDA's regulatory regime governing *autologous* stem cell procedures was *ultra vires* because *autologous* stem cell procedures carry "no risk of spreading communicable disease from foreign countries into the States or possessions, or from one State or possession into any other State or possession." (DE 16:30-32; JA 60-62).

However, in its Memorandum Opinion, at 20-21, the District Court ruled that because the FDA said in a regulatory preamble that both autologous and allogeneic procedures carry some risk of spreading communicable disease, the FDA "acted within the authority granted by section 361 of the PHSA." (DE 47:21; Addendum 1; JA 944) (Memorandum Opinion, at 21; *citing* 69 Fed.Reg. at 68,613). Although the District Court did not say so in its Opinion, this ruling endorsed the Government's theory of "broad authority vested in FDA to issue regulations to prevent the transmission of communicable disease and FDA's considered determination that the regulations in 21 C.F.R. Part 1271 are necessary to prevent the transmission of communicable diseases…" (DE 20:53).

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As the Government did in arguing its position, the District Court ignored critical statutory and regulatory language when considering the FDA's jurisdiction to write the Part 1271 regulations.

In this case, the delegation of authority that FDA implemented when writing the Part 1271 regulations is found at 42 U.S.C. § 264. That statute contains ***two*** sections which are critical to this analysis. First, § 264(a) provides in pertinent part as follows:

> The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases ***from foreign countries into the States or possessions, or from one State or possession into any other State or possession.***

(emphasis added). Additionally, § 264(e) provides as follows:

> **Preemption**. Nothing in this section or section 266 of this title, or the regulations promulgated under such sections, may be construed as superseding any provision under State law (including regulations and including provisions established by political subdivisions of States), except to the extent that such a provision conflicts with an exercise of Federal authority under this section or section 266 of this title.

Clearly, Congress did not intend for such regulations to preempt State law.[25]

[25] Of course, even if Congress had neglected to include a preemption provision in § 264, the effect would likely be the same: "Even when Congress has undoubted power to pre-empt local law, we have wisely decided that 'unless Congress conveys its purpose clearly, it will not be deemed to have significantly changed the

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In this case, the Government argued (and the District Court agreed) that it had the jurisdiction to regulate autologous stem cell procedures because "regardless of whether the cells or tissues are for autologous or allogeneic use, they are susceptible to, *inter alia*, improper labeling, a mix up with other cells, contamination, cross-contamination, and accidental exposure to communicable disease agents." (DE 20:39-40) (*citing* 69 Fed.Reg. 68613).

As compelling as its argument may be at first glance, it is not sufficient to make a Federal case out of the Procedure. First, as FDA has itself articulated, "the risk of disease transmission from such activities is believed ***minimal***" and thus communicable disease testing is not necessary." 64 Fed.Reg. 52715; (emphasis added). This is true regardless of the extent to which the cells are to be manipulated. Accordingly, the 1271 regulations themselves "do not require manufacturers to determine the eligibility of donors for cells or tissues for autologous use." (DE 20:38-39) (*citing* 21 C.F.R. § 1271.90(a)(1)). Thus, given this "minimal" risk, the Government and the District Court are hard pressed to now say that State police powers are insufficient and that Federal regulation, triggered by some unspecified interstate nexus, is required.

Next, as § 264 makes clear, the issue is not simply whether the autologous use of stem cells leads to a risk of spreading communicable diseases. Rather, the

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federal-state-balance.'" *Jones v. United States*, 529 U.S. 848, 859 (2000) (Stevens, J., concurring); *quoting*, *United States v. Bass*, 404 U.S. 336, 349 (1971).

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issue is whether the autologous use of stem cells leads to a risk of spreading communicable diseases ***from foreign countries into the States or possessions, or from one State or possession into any other State or possession***; 42 U.S.C. § 264(a). Neither the Government nor the District Court ever address how autologous procedures might cause the spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. To ignore this language as the District Court did in its Opinion is to violate the "endlessly reiterated principle of statutory construction…that all words in a statute are to be assigned meaning, and that nothing therein is to be construed as surplusage." *Qi-Zhuo v. Meissner*, 70 F.3d 136, 139 (D.C. Cir. 1995); *see also Chaney*, 718 F.2d at 1199 (Scalia, J., dissenting) ("…it is always improper – and opens the gates much more widely to judicial abuse – to ignore intentional statutory language.")

The position shared by the Government and District Court must also fail because it infringes upon the practice of medicine. Indeed, it is well settled that when Congress chooses to regulate something traditionally left for the States to regulate, it does so with explicit language in the statute; *see e.g. Gonzales v. Oregon*, 546 U.S. at 272. In this case, the delegation of authority behind the Part 1271 regulations is neither silent nor ambiguous on this issue; instead, it

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specifically states that regulations promulgated pursuant to such authority should not supersede State law; 42 U.S.C. § 264(e).

In its Motion to Dismiss, at 37, the Government further argued that "because section 361 of the PHSA is remedial legislation aimed at protecting the public health, it is entitled to liberal construction." (DE 20:37) (*citing United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). It is unclear if the District Court endorsed this argument. Either way, *Bacto-Unidisk* does not alter this analysis, as the Court in that case held as follows:

> In upholding the Secretary's construction of the Act, we are not unmindful of our warning that "in our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop." Our holding here simply involves an obvious corollary to that principle, that we must take care not to narrow the coverage of a statute short of the point where Congress indicated it should extend.

Id., at 737-738; *quoting 62 Cases of Jam v. United States*, 340 U.S. 593, 600 (1951); *see also Brown & Williamson Tobacco Corp.* 529 U.S. at 161. *Bacto-Unidisk* does not create a new canon of statutory construction; instead, it is consistent with *Gonzales v. Oregon*, *ABA v. FTC*, *Brown & Williamson Tobacco Corp*. and lends no support to the Government's expansive interpretation of its own authority.

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For all of these reasons, the District Court's Order granting the Government's motion to dismiss should be reversed.

III. THE DISTRICT COURT'S ORDER PERMANENTLY ENJOINING THE APPELLANTS WAS ENTERED IN ERROR.

A. The Injunction Order

Contemporaneously with its Memorandum Opinion, the District Court entered an Injunction Order which was merely an endorsement of a wish list authored by the Government. Indeed, the same document signed by the District Court was submitted by the Government as an attachment to its Motion for Summary Judgment; *see* (DE 19-8; JA 77-88). Moreover, in entering its Injunction, the District Court made no recorded findings that the Appellants needed to be enjoined or that the individual terms of the injunction were appropriate. How the District Court went about this process was fundamentally erroneous.

B. Standard of Review

While this Court reviews district court conclusions of law *de novo*, "[t]o the extent it is not based on legal error, we review the district court's decision to issue an injunction for abuse of discretion." *United States v. Philip Morris USA, Inc.*, 566 F.3d 1095, 1110 (D.C. Cir. 2009); *citing SEC v. Wash. Inv. Network*, 475 F.3d 392, 399 (D.C. Cir. 2007). Furthermore, even in cases where – as here – the District Court adopts a party's proposed findings verbatim, this Court will "not set

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aside the district court's findings of fact unless they are clearly erroneous, giving due regard to the court's opportunity to judge the witnesses' credibility." *Id., citing Anderson v. City of Bessemer City*, 470 U.S. 564, 572 (1985); Fed.R.Civ.P. 52(a)(6).

Ordinarily, "[i]f the record below does not permit a confident assessment of the trial court's findings, the proper course for an appellate court is to remand for further factfinding, not to engage in its own guesswork." *Berger v. Iron Workers Reinforced Rodmen Local 201*, 843 F.2d 1395, 1407 (D.C. Cir. 1998). However, where – as here – a district court "abdicates to a party his duty to provide a reasoned explanation for his decision and merely copies submitted proposals," this Court's "function of appellate review is substantially different (and more difficult) than what is normally required." *Berger*, 843 F.2d at 1407; *citing Southern Pacific Communications Co., et al v. AT&T*, 740 F.2d 980, 984 (D.C. Cir. 1984). Indeed, in such cases, "it is incumbent on this Court to check the adopted findings against the record 'with particular, even painstaking, care.'" *Id., citing Southern Pacific*, 740 F.2d at 984. As this Court has explained:

> The "special care" we devote to reviewing "findings [that] were not initially penned by the district judge," differs from that which we ordinarily display, not in the test that we apply to a particular finding of fact…but in the volume of evidence we sift in judging the correctness of such findings and in the number of discrete findings we review without benefit of express, thoroughly supported allegations of error by the opposing party.

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Id., quoting Valentino v. United States Postal Serv., 674 F.2d 56, 60 n.2 (D.C. Cir. 1982).

C. The District Court's Factual Finding that an Injunction was Necessary was Clearly Erroneous

In order to "obtain equitable remedies, the government must demonstrate a "reasonable likelihood of further violation[s] in the future." *Philip Morris,* 566 F.3d at 1132; *citing SEC v. Savoy Indus., Inc.,* 587 F.2d 1149 (D.C. Cir. 1978). As this Court has stated, "[c]onsidered under the totality of the circumstances, three factors determine whether a reasonable likelihood exists: 'whether a defendant's violation was isolated or part of a pattern, whether the violation was flagrant and deliberate or merely technical in nature, and whether the defendant's business will present opportunities to violate the law in the future.'" *Philip Morris*, 566 F.3d at 1132; *quoting SEC v. First City Fin.Corp.* 890 F.2d 1215, 1228 (D.C. Cir. 1989).

Unfortunately, rather than making any findings regarding these factors, the District Court simply wrote in its Injunction Order that it "found…the [Appellants], unless restrained by order of this Court, will continue to violate the FDCA." (DE 48:1; Addendum 2; JA 946). This was simply not enough.

First, in the years leading up to this case, the Defendants showed the utmost respect for the judicial system, and sought the jurisdiction of the Courts on multiple occasions to resolve the dispute between the parties; Memorandum

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Opinion, at p.5. On both occasions, when the Defendants sought a determination as to whether they were in violation of the law, *the Government* sought to prevent those suits from going forward on the grounds that they were unripe. But for these motions, the question of whether the Procedure constituted the practice of medicine would have been resolved years ago.

Next, the Government alleged that "Defendants are manufacturing an injectable biological drug product in a manner that does not comply with CGMP, thereby posing significant risks to the consumers who receive it." (DE 19:38). However, as previously stated, while cGMP is applicable to the manufacturing of drugs, it is not applicable to the practice of medicine, which the Appellants believe in good faith the Procedure to be; DE 26, at 36; *see also* Henderson Affidavit, (DE 26-20:¶3; JA 820) (comparing Appellants' safety protocols to those used in in-vitro fertilization procedures); Angle Affidavit, (DE 26-21:¶13-14; JA 836) (same, concluding that "the methods employed in IVF labs…are not nearly as extensive as the ones used routinely by" Appellants). Likewise, in the case below, the Government offered no evidence of any patient ever being harmed by the Procedure, and failed to articulate why the Appellants' robust safety protocols were insufficient to protect their patients. Thus, the Government's allegations regarding cGMP were technical in nature, and did not warrant a permanent injunction; *Philip Morris*, 566 F.3d at 1132.

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The Government also alleged that the Appellants were experimenting on their patients by treating them with a drug that was not the subject of "adequate and well-controlled clinical trials..." (DE 19:38-39). It is unclear, however, whether this allegation factored into the District Court's decision to permanently enjoin the Appellants. To the extent that it did, the District Court should have also considered the Appellants' compliance with *The Belmont Report*. Indeed, *The Belmont Report* provides a tutorial regarding what constitutes the practice of medicine, what constitutes medical research, what constitutes a combination of the two, and how the physician should govern himself in each of those circumstances; *see* Centeno Affidavit, (DE 26-8:¶¶116-126;JA 507-512). The District Court made no mention of *The Belmont Report* at any time and thus erred when entering its Order of Permanent Injunction.

Given all of these factors, especially when coupled with the Appellants' untarnished medical records,[26] there was no reasonable likelihood that a repeat violation would occur. As such, the permanent injunction entered in this case was an unnecessary exercise of the Court's equitable powers, and should be reversed on appeal.

[26] *See,* Centeno Affidavit, (DE 26-7:¶2; JA 443).

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CONCLUSION AND PRAYER FOR RELIEF

For the foregoing reasons, we respectfully submit that this Court should reverse the decision of the District Court, strike the Order of Permanent Injunction, enter an Order finding the Procedure to be the practice of medicine as defined by Colorado law, and rule that FDA's Part 1271regulations are *ultra vires*, arbitrary and capricious, or both.

Dated March 15, 2013.

Respectfully Submitted,

/s/ Andrew S. Ittleman

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DESIGNATION PURSUANT TO FRAP 30(c)

Pursuant to Rule 30(c) of the Federal Rules of Appellate Procedure, Appellants designate the following parts of the record to be included in the Deferred Appendix. References are to the Docket Entry Number set out in the Docket Report of *United States v. Regenerative Sciences, LLC et al.*, Case No. 10-1327 (D.D.C. July 23, 2012): DE #1, DE #10, DE #16, DE #19, DE #19-8, DE

#20, DE #25, DE #25-1, DE #26, DE #26-1, DE #26-2, DE #26-3, DE #26-4, DE #26-5, DE #26-6, DE #26-7, DE #26-8, DE #26-9, DE #26-10, DE #26-11, DE #26-12, DE #26-13, DE #26-14, DE #26-15, DE # 26-16, DE #26-17, DE #26-18, DE #26-19, DE #26-20, DE #26-21, DE #26-22, DE #30, DE #39, DE #41, and DE #41-1.

CERTIFICATION OF COMPLIANCE WITH FED.R.APP.P. 32(a)(7)(C) AND D.C. CIRCUIT RULE 32-1

I certify that pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C) and D.C. Circuit Rule 32(a)(1), the attached opening brief is proportionately spaced, has a typeface of 14 points or more and contains13,958 words.

/s/ Andrew S. Ittleman
Andrew S. Ittleman, Esq.
Attorney for Appellants

CERTIFICATE OF SERVICE

I hereby certify that on March 15, 2013, a true and correct copy of the foregoing was served electronically via CM/ECF to the opposing counsel:

/s/ Andrew S. Ittleman
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ADDENDUM 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, **Plaintiff,** **v.** **REGENERATIVE SCIENCES, LLC, CHRISTOPHER J. CENTENO, M.D., JOHN R. SCHULTZ, M.D., and MICHELLE R. CHEEVER,** **Defendants.**	**Civil Action No. 10-1327 (RMC)**

MEMORANDUM OPINION

Drs. Christopher J. Centeno and John R. Schultz developed the Regenexx™ Procedure, by which they use stem cell therapies to aid healing for their orthopedic patients. They formed Regenerative Sciences LLC ("Regenerative") for this endeavor, at which Michelle R. Cheever is the Laboratory Director. They are all now facing an enforcement action by the Food and Drug Administration ("FDA"), which charges them with "causing articles of drug to become adulterated" and "misbranded" within the meaning of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq.* Compl. [Dkt. 1] ¶ 1. Defendants respond that they practice medicine wholly within the State of Colorado and under its oversight and that the Regenexx™ Procedure is not a "drug" subject to regulation by the federal government. Defs.' Opp. to Pl.'s Mot. for Summ. J. [Dkt. 26] ("Defs.' Opp") at 1.

It is a close question but ultimately the Court concludes that the Regenexx™ Procedure is subject to FDA enforcement because it constitutes a "drug" and because a drug that has been shipped in interstate commerce is used in the solution through which the cultured stem cells are administered to patients. This acknowledged connection to interstate commerce renders the Regenexx™ Procedure subject to the FFDCA even though the doctors themselves are practicing medicine under Colorado law. Summary judgment will be granted to the United States and an injunction will be issued precluding the continued use of the Regenexx™ Procedure without compliance with the FFDCA.

I. FACTS

Drs. Centeno and Schultz practice together and jointly own the Centeno-Schultz Clinic in Broomfield, Colorado. Drs. Centeno and Schultz are also the majority shareholders of Regenerative, which owns the Regenexx™ Procedure and exclusively licenses the Clinic to use it. Ms. Sheever serves as Regenerative's Laboratory Director. Regenerative and the Clinic are related companies and operate as one business. The Regenexx™ Procedure is a non-surgical procedure for patients suffering from moderate to severe joint, muscle, tendon or bone pain due to injury or other conditions. Am. Answer Countercls. [Dkt. 16] ("Countercls.") ¶ 3.

> The Regenexx™ Procedure begins with a licensed physician taking a small bone marrow sample from the back of a patient's hip through a needle. Blood samples are also taken from a vein in the patient's arm. These samples are then sent to the Regenerative laboratory which is also in Broomfield, Colorado, just a few miles from the Clinic where the mesenchymal stem cells (MSCs) are isolated from the bone marrow and then grown to greater numbers. This process uses the natural growth factors found in the patient's blood to grow the MSCs.
>
> After approximately 2 weeks, the expanded stem cells are sent to the University of Colorado affiliated Colorado Genetics Laboratory for testing. . . .

> Once the cells pass quality assurance testing, they are placed back into the patient's injured area (i.e. knee, hip, rotator cuff), typically 4-6 weeks after they were removed. The stem cells then begin to repair the patient's degenerated or injured area. The repair process usually takes between 3-6 months but many patients demonstrate marked improvement within 1-3 months.

Countercls. ¶¶ 5-10. In August 2010, when this matter began, the Regenexx™ Procedure constituted about one-third of the procedures performed by the Clinic. Defs.' Opp. at 15.

Of critical importance here is the process by which Regenerative expands the mesenchymal cells taken from a patient's bone marrow and delivers a syringe with the cells in solution to the Clinic.

> 1. A doctor at the Clinic obtains a tissue sample from the patient's bone marrow by inserting a needle into the hip bone and drawing a thick blood like liquid into a syringe; the sample is then sent to the laboratory.
>
> 2. The marrow sample is centrifuged to separate out fractions of the bone marrow and the middle layer ("buffy coat") is taken off with a pipette.
>
> 3. The cells from the buffy coat are placed in a plastic flask and kept in a warm environment to incubate with the patient's own blood platelets that contain growth factors, as well as a nutrient solution. Over a few days, the mesenchymal stem cells adhere to the plastic flask while the rest of the cells do not adhere.
>
> 4. The non-adherent cells are discarded and the mesenchymal stem cells are collected using Trypsin, an enzyme, to detach the cells from the plastic flask.
>
> 5. The process is repeated to grow the cells.
>
> 6. The cells undergo a visual inspection by the Colorado Genetics Laboratory to make sure that there are no genetic mutations or other genetic problems. The treating doctor then approves the cells.

Defs.' Opp., Ex. 7 [Dkt. 26] (Centeno Decl.) ¶¶ 13-24; *see also* Compl. ¶ 11. "[T]he expanded cells, along with a drug product that has been shipped in interstate commerce[1] and other additives, are placed into syringes. Regenerative Sciences [sends] the filled syringes in sterile bags to the Clinic, where they are injected into patients." Compl. ¶ 11; *see* Answer ¶¶ 11 & 13 (admitting this fact).

In a letter dated July 25, 2008, the FDA notified Regenerative that the FDA believed that the cell product used in the Regenexx™ Procedure constituted a drug under the FFDCA and a biological product under the Public Health Service Act, 42 U.S.C. § 262 ("PHSA"). Further, the FDA stated that because Regenerative had not obtained the necessary approvals for the cell product, its actions in this regard were possibly unlawful. Countercls. ¶¶ 20 & 21; Pl.'s Mot. for Summ. J. [Dkt. 19] ("Pl.'s Mot.") at 13.

FDA investigators inspected Regenerative between February 23, 2009 and April 15, 2009. Compl. ¶ 31; Countercls. ¶ 24. That inspection showed that the laboratory did not operate in conformity with current good manufacturing practice ("CGMP").[2] *See* 21 U.S.C. § 351(a)(2)(B) and 21 C.F.R. Parts 210-211; *see also* 21 C.F.R. Parts 600-680. When the 2009 inspection concluded, the FDA investigators issued a list of observations that identified a series of alleged CGMP violations. Compl. ¶ 31.

FDA investigators again inspected Regenerative between June 2, 2010 and June 16, 2010. Countercls. ¶¶ 26, 27. That inspection also revealed alleged CGMP violations, which the investigators catalogued in a list of observations. Compl. ¶ 32.

---

[1] The "drug product" is not identified except in sealed documents as Defendants claim it is confidential commercial information. *See* Pl.'s Mot. at 12 n.14.

[2] CGMP "assure[s] that [a] drug meets the requirements of [the statute] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(2)(B).

While the initial FDA inspection was ongoing, Regenerative filed a complaint against the FDA in United States District Court for the District of Colorado, alleging that the FDA did not have the jurisdiction to regulate autologous[3] use of stem cells. *Regenerative Sciences, Inc. v. FDA*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 1] (D. Colo. Feb. 26, 2009) ("*Regenerative I*"). On March 26, 2010, the district court granted the FDA's motion to dismiss on ripeness grounds. *Regenerative I*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 42] (D. Colo. Mar. 26, 2010). Regenerative then filed a notice of appeal with the United States Court of Appeals for the Tenth Circuit on March 29, 2010.[4] *Regenerative I*, Civ. No. 10-1125 (10th Cir.).

On June 22, 2010, Regenerative filed a complaint in this Court challenging FDA's determination that Regenerative is a drug manufacturer. *Regenerative Sciences, Inc. v. FDA*, Civ. No. 1:10-cv-01055 [Dkt. 1] (D.D.C. June 22, 2010) ("*Regenerative II*"). On July 6, 2010, Regenerative filed a motion for a temporary restraining order in this Court. *Regenerative II*, Civ. No. 1:10-cv-01055 [Dkt. 9] (D.D.C. July 6, 2010). Pursuant to a Stipulated Order, the parties agreed to litigate the entire dispute in this Court. Defs.' Opp. at 19-20. Accordingly, Regenerative agreed to dismiss the pending actions in the District of Colorado and the Tenth Circuit, as well as withdraw its motion for a temporary restraining order in this Court. Stip. Order [Dkt. 10] at ¶ 11. Regenerative also agreed to stop using the Regenexx™ Procedure during the pendency of this litigation. *Id.* at ¶ 6. FDA has filed a motion for summary judgment, as well as a motion to dismiss Defendants' counterclaims.

[3] "Autologous use means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." 21 C.F.R. § 1271.3.

[4] On June 30, 2010, Regenerative filed a motion to stay the Colorado case pending its appeal. *Regenerative I*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 53] (D. Colo. June 30, 2010).

II. LEGAL STANDARDS

A. Summary Judgment

Under Rule 56 of the Federal Rules of Civil Procedure, summary judgment shall be granted "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *accord Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247 (1986); *Talavera v. Shah*, 638 F.3d 303, 308 (D.C. Cir. 2011). Moreover, summary judgment is properly granted against a party who "after adequate time for discovery and upon motion . . . fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

In ruling on a motion for summary judgment, the court must draw all justifiable inferences in the nonmoving party's favor and accept the nonmoving party's evidence as true. *Anderson*, 477 U.S. at 255; *Talavera*, 638 F.3d at 308. A nonmoving party, however, must establish more than "[t]he mere existence of a scintilla of evidence" in support of its position. *Anderson*, 477 U.S. at 252. In addition, the nonmoving party may not rely solely on allegations or conclusory statements. *Greene v. Dalton*, 164 F.3d 671, 675 (D.C. Cir. 1999). Rather, the nonmoving party must present specific facts that would enable a reasonable jury to find in its favor. *Id.* If the evidence "is merely colorable, or is not significantly probative, summary judgment may be granted." *Anderson*, 477 U.S. at 249-50 (citations omitted).

B. Motion to Dismiss

A motion to dismiss for failure to state a claim pursuant to Federal Rule of Civil Procedure 12(b)(6) challenges the adequacy of a complaint on its face. Fed. R. Civ. P. 12(b)(6). A complaint must be sufficient "to give the defendant fair notice of what the . . . claim is and the

grounds upon which it rests." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555 (2007) (internal quotation marks and citation omitted). Although a complaint does not need detailed factual allegations, a plaintiff's obligation to provide the grounds of his entitlement to relief "requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Id.* To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to state a claim for relief that is "plausible on its face." *Twombly*, 550 U.S. at 570.

A court must treat the complaint's factual allegations as true, "even if doubtful in fact." *Twombly*, 550 U.S. at 555. But a court need not accept as true legal conclusions set forth in a complaint. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). In deciding a motion under Rule 12(b)(6), a court may consider the facts alleged in the complaint, documents attached to the complaint as exhibits or incorporated by reference, and matters about which the court may take judicial notice. *Abhe & Svoboda, Inc. v. Chao*, 508 F.3d 1052, 1059 (D.C. Cir. 2007).

III. ANALYSIS

The question presented here is whether the Regenexx™ Procedure constitutes a drug (or biologic product) subject to FDA regulation or whether it is merely an intrastate method of medical practice subject only to the laws of the State of Colorado. FDA asserts that the Regenexx™ Procedure constitutes the manufacturing, holding for sale, and distribution of an unapproved biological drug product. Moreover, FDA claims that Defendants have violated the FFDCA's prohibition on adulteration and misbranding a drug with their Regenexx™ Procedure. On the other hand, Defendants argue that the Regenexx™ Procedure constitutes the practice of medicine as defined by Colorado law and that the FDA lacks jurisdiction to regulate it.

Defendants also assert that the Regenexx™ Procedure occurs entirely intrastate and is not covered by the Commerce Clause or the FFDCA, which limit federal power to interstate commerce.

A. Federalism and the Commerce Clause

Defendants insist that the FDA's complaint must be understood within the constitutional principles of federalism and the limits of the Commerce Clause. They urge the Court to apply the "assumption that the historic police powers of the States were not to be superseded by [a] Federal Act unless that was the clear and manifest purpose of Congress." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (internal quotation marks and citations omitted). By long tradition, the health and safety of the people is left to the States as matters of local concern. *Id.* at 475. Accordingly, Defendants state that Congress has left the practice of medicine to the States to regulate. FDA does not disagree with these principles but asserts that their exercise of jurisdiction over Defendants' Regenexx™ Procedure is a permissible exercise of federal power under the Commerce Clause.

Congress may regulate the practice of medicine or rather, certain aspects of it, when it does so pursuant to its Commerce Clause powers. Congress has the power "[t]o regulate Commerce . . . among the several states . . . ." U.S. Const. art. I, § 8, cl. 3. The United States Supreme Court has defined three categories of activity that may be regulated by Congress pursuant to its Commerce Clause power: (1) "channels of interstate commerce," (2) "instrumentalities of interstate commerce, or persons or things in interstate commerce," (3) "those activities having a substantial relation to interstate commerce," or "those activities that substantially affect interstate commerce." *United States v. Lopez*, 514 U.S. 549, 558-59 (1995).

> The [FFDCA] rests upon the constitutional power resident in Congress to regulate interstate commerce. To the end that the

> public health and safety might be advanced, it seeks to keep interstate channels free from deleterious, adulterated and misbranded articles of the specified types. It is in that interstate setting that the various sections of the Act must be viewed.

United States v. Walsh, 331 U.S. 432, 434 (1947) (internal citations omitted). The FFDCA provisions at issue in this case require an interstate commerce nexus, ensuring that regulation under the FFDCA is consistent with the Commerce Clause. 21 U.S.C. § 331(k) (applying only if the drug is held for sale "after shipment in interstate commerce"). Thus, the question here is one of statutory interpretation – whether Defendants' cell product is subject to the terms of the FFDCA.

B. The Regenexx™ Procedure is a "Drug" Under the FFDCA

1. Definition of a "Drug"

The best place to start when interpreting a statute is the language of the law itself. *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 450 (2002) ("As in all statutory construction cases, we begin with the language of the statute."). The FFDCA defines "drug" to mean "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(B)&(C). Based on this definition, whether an "article" is a "drug" depends on its "intended use." *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) is binding precedent on this point:[5] under the FFDCA, "classification of a substance as a 'drug' turns on the nature of the claims advanced on its behalf."[6] Further, "it is well established

[5] The Court asked the parties "why the Court should not read the definition of 'device' at 21 U.S.C. § 321(h) as informing and restricting the definition of 'drug' at 21 U.S.C. § 321(g)(1)(B)&(C)" and is now persuaded to adopt the direct language of the statute without interpretation. Order to Show Cause [Dkt. 42].

[6] *See also United States v. Writers & Research, Inc.*, 113 F.3d 8, 11 (2d Cir. 1997) ("Regardless of the classification of a drug, if an article is intended for use in the diagnosis, cure, mitigation,

that the intended use of a product, within the meaning of the [FFDCA], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (internal quotation marks and citations omitted); *see* 21 C.F.R. § 201.128 ("The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article . . . ." (emphasis added)); *Estee Lauder, Inc. v. FDA*, 727 F. Supp. 1, 2 (D.D.C. 1989) ("Courts have held that the decision as to whether a product is a drug depends on its 'intended use,' which can be determined from objective evidence such as the product's current and past containers, instructions, and advertisements.").

FDA also regulates biological products under the PHSA, 42 U.S.C. § 262. A "biologic product" is defined by the PHSA as any "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). A product may be both a drug and a biological product. *See, e.g., CareToLive v. von Eschenbach*, 525 F. Supp. 2d 952, 957 (S.D. Ohio 2007).[7] Except for some licensing distinctions, the FFDCA applies in full to a biologic product licensed under the PHSA. 42 U.S.C. § 262(j); *see*

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treatment, or prevention of disease in man it is defined as a drug."); *Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 333 (2d Cir. 1977) ("The vendors' intent in selling the product to the public is the key element in this statutory definition.").

[7] *See also United States v. Loran Med. Sys., Inc.*, 25 F. Supp. 2d 1082, 1084-1087 (C.D. Cal. 1997) (holding that a cell product made from neonatal rabbit and human fetal cells was both a drug and a biological product).

CareToLive, 525 F. Supp. 2d at 957 ("Biological products . . . are generally subject to the same statutory and regulatory requirements that apply to drugs.").

Defendants' website and pleadings describe their "intended use" for the Regenexx™ Procedure. Defendants promote the Regenexx™ Procedure to treat a variety of orthopedic conditions and injuries. On the Regenerative Sciences' website, www.regenexx.com, Defendants describe the Regenexx™ Procedure as "an Alternative to Traditional Surgery" that can treat "[f]ractures that have failed to heal, joint cartilage problems, partial tears of tendons, muscles, or ligaments, chronic bursitis, avascular necrosis of the bone, and lumbar disc bulges." *See* Answer ¶ 16.b.

Defendants' pleadings confirm their intentions to use the Regenexx™ Procedure for "mitigation" and "treatment," among others, of disease and injury. They explain how the "stem cells . . . begin to repair the patient's degenerated or injured area," Countercls. ¶ 10; how the Regenexx™ Procedure is "for the treatment of orthopedic injuries and arthritis," *Regenerative II*, Civ. No. 1:10-cv-01055 [Dkt. 1] (D.D.C. June 22, 2010) (Compl. ¶ 14); and how "[t]he Procedure is for the treatment of musculoskeletal and spinal injury." *Regenerative I*, Civ. No. 09-cv-00411-WYD [Dkt. 1] (D. Colo.) (Compl. ¶ 16). These statements of "intended use" fully satisfy the statutory definition for a "drug." Similarly, Defendants' admissions that the Regenexx™ Procedure is based on mesenchymal stem cells derived from the patient's bone marrow (Countercls. ¶ 5) and that it is intended to treat orthopedic conditions fully satisfy the definition of "biological product" under the PHSA because it is a "blood, blood component or derivative, . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i); *see* Pl.'s Mot., Ex. C (Shannon

Dec.) ¶ 9. In sum, the cell product used in the Regenexx™ Procedure meets the statutory definition for both a "drug" under the FFDCA and a "biological product" under the PHSA.

2. The Regulations at 21 C.F.R. Part 1271 Do Not Exempt the Regenexx™ Procedure

The FDA has the authority under the PHSA to enact regulations to prevent the spread of communicable diseases. Section 361 of PHSA, 42 U.S.C. § 264(a), states that

> The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.

Although this section grants this authority to the Surgeon General, it now rests with the FDA.[8]

The development of research and medical treatments using human cells, tissues, and cellular or tissue-based products (human cell or tissue products or "HCT/Ps") caused the FDA to announce in 1997 a tiered, risk-based approach for their regulation. *See* Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997) (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf. In 2001, after notice and comment, the FDA issued the first of a set of regulations pertaining to HCT/Ps pursuant to its authority under section 361 of the PHSA. *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule, 66 Fed. Reg. 5447 (Jan. 19, 2001) ("Registration Rule").[9] The regulations created a new regulatory

[8] *See infra* Section III. E.

[9] *See also* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule, 69 Fed. Reg. 29,786 (May 25, 2004); Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments;

framework for HCT/Ps "to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products." *Id.* at 5447. Part 1271.3 defines HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d). Those HCT/Ps that meet the set of criteria listed in 21 C.F.R. § 1271.10 are only regulated under section 361 of the PHSA and Part 1271 of the C.F.R. In contrast, those HCT/Ps that do not meet these criteria are regulated as "a drug, device, and/or biological product." 21 C.F.R. § 1271.20.

One of these criteria is that the HCT/Ps be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). Minimal manipulation is defined as "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2). Defendants admit that "[t]he processing of the cultured cell product involves many steps, including selective culture and expansion of a multitude of different types of blood-forming and rare bone marrow stromal cells using plastic flasks, additives and nutrients, and environmental conditions such as temperature and humidity, to determine the growth and biological characteristics of the resulting cell population." Pl.'s Statement of Material Facts [Dkt. 19] ("Pl.'s SMF") ¶ 10; Defs.' Resp. to Pl.'s SMF [Dkt. 26] ¶ 10. This admission supports the conclusion that the biological characteristics of the cells change during the process employed by Defendants, resulting in more than minimal manipulation of the HCT/Ps originally extracted from the patient. Moreover, the FDA's conclusion that the Regenexx™ Procedure does not meet the regulatory definition of "minimal manipulation" is entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see also Petit v. Dep't of Educ.*, 675 F.3d 769, 778 (D.C. Cir.

Inspection and Enforcement; Final Rule, 69 Fed. Reg. 68,612 (Nov. 24, 2004) ("Good Practice Rule").

2012) (citing the deference afforded to an agency's interpretations of its own regulations); *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) ("The rationale for deference is particularly strong when the [agency] is evaluating scientific data within its technical expertise . . . .") (internal quotations marks and citation omitted) (alteration in original)). As a result, Defendants fail to meet at least one of the criteria listed in 21 C.F.R. § 1271.10, and the HCT/Ps in the Regenexx™ Procedure must be regulated as a "drug" under the FFDCA.

C. Defendants Violated 21 U.S.C. § 331(k)

1. The Regenexx™ Procedure Is Subject to the Commerce Clause

The FFDCA prohibits any act "with respect to, a . . . drug . . . , if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated for misbranded." 21 U.S.C. § 331(k). FDA alleges that Defendants have violated § 331(k) by both adulterating and misbranding a drug. To prevail on this claim, the FDA must first establish that the cell product used in the Regenexx™ Procedure was both (1) "held for sale" and prior to such sale had been (2) "ship[ped] in interstate commerce." The cell product meets both of these requirements.

Concerning the first element, "a doctor who ha[s] held drugs for use in his practice ha[s] held those drugs for sale within the meaning of [§ 331(k)]." *United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. April 1981); *see also United States v. Sullivan*, 332 U.S. 689, 697 (1948) (interpreting the statute to cover "every article that ha[s] gone through interstate commerce until it finally reache[s] the ultimate consumer."); *United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975) (holding that § 331(k) covers medical devices held by practitioners used for the treatment of their patients). Defendants create the cell product, the "drug" in this case, and use it to treat their patients. Such conduct satisfies the "held for sale" requirement of the statute.

Defendants do not contest the "held for sale" requirement but instead argue that the Regenexx™ Procedure does not meet the "interstate commerce" requirement because the entire process takes place intrastate at Defendants' medical facilities in Colorado. The FFDCA defines "drug" to include "articles intended for use as a *component* of any article . . . ." 21 U.S.C. § 321(g)(1)(D)(emphasis added). Courts have held that the "interstate commerce" element is met if any component of that drug moved in interstate commerce. *See Baker v. United States*, 932 F.2d 813, 816 (9th Cir. 1991) ("We hold that wholly intrastate manufacturers and sales of drugs are covered by 21 U.S.C. § 331(k) as long as an ingredient used in the final product travelled in interstate commerce."); *Dianovin Pharmaceuticals, Inc.*, 475 F.2d 100, 103 (1st Cir. 1973) ("The appellants' use of components shipped in interstate commerce to make vitamin K for injection brought their activities within § 331(k) . . .). Defendants combine an antibiotic, doxycycline, with the cell product before the drug is administered to the patients through a syringe. Pl.'s SMF ¶ 23; Def.'s Resp. to Pl.'s SMF ¶ 23. Defendants do not dispute that the doxycycline is shipped from out of state to their facilities in Colorado. *Id*. Therefore, because a component of the drug in this case is shipped through interstate commerce prior to its administration to the patient, the "interstate commerce" requirement is also met.

2. Adulteration

The FDA claims that Defendants have adulterated and misbranded their drug in violation of the FFDCA. Under the terms of the FFDCA, a drug is adulterated "if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice . . . ." 21 U.S.C. § 351(a)(2)(B). "Drugs produced in violation of these CGMP regulations are deemed to be adulterated without the agency having to show that they are

actually contaminated." *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988). Although Defendants claim that the Regenexx™ Procedure is not subject to the FFDCA, they admit that the procedure does not comply with CGMP. Answer ¶¶ 31, 32. The FDA performed two separate inspections, one in 2009 and the other in 2010, which revealed a number of CGMP violations. *Id.* Having concluded that the cell product used in the Regenexx™ Procedure is a "drug" that is subject to regulation by the FFDCA and that the drug has been "held for sale after shipment in interstate commerce," the fact that the Regenexx™ Procedure does not comply with CGMP renders the drug adulterated in violation of the FFDCA.

3. Misbranding

The FDA also claims that Defendants have violated the FFDCA by misbranding the cultured cell product. The FDA asserts that the cultured cell product is misbranded because it is a prescription drug that does not bear the "Rx only" symbol or carry "adequate directions for use." Under the FFDCA, a prescription drug is one which "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug ." 21 U.S.C. § 353(b)(1)(A). Once Defendants' cell product is ready to be used for treatment, it is administered by injection using a type of x-ray device for guidance. Pl.'s SMF ¶ 13; Def.'s Resp. to Pl.'s SMF ¶ 13. Given the drug's "method of use" and the "collateral measures necessary to its use," administration of the drug can only safely take place under the supervision of a specially-trained practitioner. Thus, the cultured cell product is a prescription drug under the terms of the statute.

A prescription drug is misbranded "if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol "Rx only." 21 U.S.C. § 353(b)(4)(A). It is

undisputed that the label of the cultured cell product does not bear this symbol. Pl's SMF ¶ 17; Def's Resp. to Pl's SMF ¶ 17. On this basis, Defendants misbrand the cultured cell product in violation of the FFDCA.

The FDA further alleges that Defendants have misbranded the cultured cell product because its label does not bear "adequate directions for use," which the FFDCA requires. 21 U.S.C. § 352(f)(1) . The FDA defines "adequate directions for use" as "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. However, a prescription drug by its very definition cannot bear "adequate directions for use" by a layman. As a result, a prescription drug must qualify for an exemption to avoid violating the FFDCA's misbranding provision. *See United States v. Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980) ("Since a prescription drug by definition can be used only under a physician's supervision, and is unsuitable for self-medication, such a drug must qualify for a regulatory exemption created by FDA, pursuant to the authority of section 352(f).").

There are two principal exemptions to the "adequate directions for use" requirement for prescription drugs. The statute provides an exemption to the misbranding provision for prescription drugs if the label contains, *inter alia*, identifying information regarding the dispenser, the prescriber, and the patient, as well as "directions for use and cautionary statements." 21 U.S.C. § 353(b)(2). This exemption, however, applies only when the drug is actually dispensed by filling a prescription of a practitioner. *Id.* The FDA has also created a regulatory exemption to the misbranding provision, which exempts prescription drugs with a label bearing, *inter alia*, information regarding dosage, administration, and ingredients. 21 C.F.R. § 201.100. In contrast to the statutory exemption, the regulatory exemption applies throughout the distribution process. *Id.*

The label for the cultured cell product contains only the "the patient's name, date of birth, laboratory notebook number, cell passage number, day in culture, cell number, number of cells cryo-preserved, and condition of cell suspension." Compl. ¶ 34: Answer ¶ 34. The information on this label does not satisfy the disclosure requirements under either the statutory or the regulatory exemptions.[10] For this reason also, Defendants have violated the misbranding provision of the FFDCA.

D. The Regenexx™ Procedure Does Not Avoid FDA Regulation Because Defendants Are Engaged in the Practice of Medicine

Defendants rely heavily on their argument that the FDA cannot regulate the Regenexx™ Procedure because it constitutes the practice of medicine. However, "[w]hile the [FFDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians." *Evers*, 643 F.2d at 1048; *see also Loran Med. Sys., Inc.*, 25 F. Supp. 2d at 1087 (dismissing defendants' "practice of medicine" argument because the court concluded that the cell product was a drug and that the FDA therefore had the authority to regulate its use). There is a difference between a licensed physician's use of an FDA-approved drug such as doxycycline in an off-label way, which is permissible within the "practice of medicine,"[11] and adding doxycycline to a cell product to be administered to patients, which renders the latter a "drug" that has connections to interstate commerce. The question of interstate commerce is not relevant to the first issue but controls the

[10] The FDA has also created a regulatory exemption for "new drugs." Section 201.115 exempts a "new drug" from the misbranding provision if "such exemption is claimed in an approved application." 21 C.F.R. § 201.115. It is undisputed that Defendants have neither sought nor has the FDA approved a new drug application for Regenexx™ Procedure. Compl. ¶. 20; Answer ¶ 20. This exemption is therefore also inapplicable.

[11] *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C.1998) ("[O]ff-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine."), *vacated in part on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

second. Likewise, the fact that off-label use of an FDA-approved drug is permissible within the practice of medicine does not speak to whether the drug traveled in interstate commerce, which provides the nexus for regulation under the provision of the FFDCA relevant here.

Where, as here, a product meets the definition of "drug" under the FDCA, it comes under the ambit of this law and is thus subject to its provisions. This is true even if its regulation will affect the practice of medicine. Consequently, Defendants' argument that the cell product cannot be regulated by the FDA because the Regenexx™ Procedure constitutes the "practice of medicine" is unavailing.

E. Defendants' Counterclaims Will Be Dismissed

In addition to its motion for summary judgment, FDA has filed a motion to dismiss Defendants' counterclaims. Counterclaims I, II, III, and VII challenge the FDA's authority to regulate the practice of medicine. These claims are dismissed for the reasons stated above. Counterclaims IV, V, and VI concern the following statement in the preamble to 21 C.F.R. § 1271: "We do not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation." Registration Rule, 66 Fed. Reg. at 5447. Counterclaims IV and V allege that this statement is arbitrary and capricious because the underlying science for the statement was never shared with the public and the statement was issued without considering all relevant factors. Counterclaim VI alleges that this statement constitutes a legislative rule that was not issued through notice and comment rulemaking.

Counterclaims IV, V, and VI arise under the Administrative Procedure Act ("APA"). *See* 5 U.S.C. §§ 553, 706(2)(A). Accordingly, Defendants can only bring the challenges in these counterclaims if the statement at issue represents "final agency action." 5 U.S.C. § 704; *see also Trudeau v. FTC*, 456 F.3d 178, 188 (D.C. Cir. 2006) (explaining that

causes of action under the APA are limited to "final agency action"). To constitute final agency action, two conditions must be met: (1) "the action must mark the consummation of the agency's decisionmaking process" and (2) it "must be one by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 177-78 (1997) (internal quotation marks and citations omitted). The challenged statement does not meet at least the latter of these two requirements because FDA's own regulations provide that statements in a preamble do not carry the force of law. *See* 21 C.F.R. § 10.85(d)(1) & (j) (stating that a preamble constitutes an advisory opinion and may be used for illustrative purposes but "not as a legal requirement"). Indeed, the D.C. Circuit recently held that a statement in a preamble did "not express a final agency action." *Am. Petroleum Inst. v. EPA*, Nos. 10-1079, 10-1080, 2012 WL 2894566, at *9 (D.C. Cir. July 17, 2012). Counterclaims IV, V, and VI are therefore dismissed.[12]

Finally, Defendants allege in Counterclaim VIII that the FDA lacks the authority to enact the "entire regulatory scheme governing stem cells" because the autologous use of stem cells carries no risk of spreading communicable diseases. As discussed above, "by delegation from the Surgeon General and the Secretary of Health and Human Services," FDA may enact regulations to prevent the spread of communicable diseases pursuant to section 361 of the PHSA, 42 U.S.C. § 264(a). *See* Good Practice Rule, 69 Fed. Reg. at 68,613. When issuing these

[12] FDA moved to dismiss on statute of limitations grounds pursuant to Fed. R. Civ. P. 12(b)(1) (subject-matter jurisdiction), as well as Fed. R. Civ. P. 12(b)(6) (failure to state a claim). The D.C. Circuit has not resolved whether the statute of limitations in 28 U.S.C. § 2401(a) is jurisdictional. *See Harris v. FAA*, 353 F.3d 1006, 1013 n.7 (D.C. Cir. 2004) (noting uncertainty regarding whether § 2401(a) is jurisdictional in light of *Irwin v. Dep't of Veterans Affairs*, 498 U.S. 89 (1990) but concluding it need not reach the issue). Because the statement in the preamble does not constitute final agency action and the counterclaims regarding the preamble must be dismissed for failure to state a claim, the Court does not reach FDA's arguments that these counterclaims are barred by the statute of limitations.

regulations, FDA carefully explained its determination that the manufacturing of HCT/Ps, including autologous stem cells, presents a risk of spreading communicable disease:

> It is important to recognize that HCT/P manufacturing inevitably has interstate effects . . . Certain diseases, such as those caused by the human immunodeficiency virus (HIV) and the hepatitis B and C viruses (HBV and HCV respectively), may be transmitted through the implantation, transplantation, infusion, or transfer of HCT/Ps derived from infected donors . . . Errors in labeling, mixups of testing records, failure to adequately clean work areas, and faulty packaging are examples of improper practices that could produce a product capable of transmitting disease to its recipient . . . [and] improper handling of an HCT/P can lead to bacterial or other pathogenic contamination of the HCT/P, or to cross-contamination between HCT/Ps, which in turn can endanger recipients.

Id. The FDA has acted within the authority granted by section 361 of the PHSA. Counterclaim VIII will be dismissed.

IV. CONCLUSION

The FDA seeks a statutory injunction to restrain Defendants' violations of the FFDCA. The FFDCA provides this court with the authority "for cause shown to restrain violations of section 331 of [the FFDCA]." 21 U.S.C. § 332(a). In the case of a statutory injunction, once the FDA has established a violation, it need only show that there is some "cognizable danger of recurrent violation." *United States v. W. T. Grant Co.*, 345 U.S. 629, 633 (1953); *see also United States v. Articles of Drug*, 825 F.2d 1238, 1248 (8th Cir. 1987) ("A district court may issue an injunction if it concludes that the injunction is necessary to prevent future violations."). FDA notified Defendants that their Regenexx™ Procedure may be in violation of the FFDCA. It then twice inspected Defendants' laboratories and found a number of CGMP violations. Defendants maintained that the FDA could not regulate their cell product and did not bring their processes into compliance with CGMP. Although Defendants agreed to stop

using their Regenexx™ Procedure during the pendency of this lawsuit, there remains a "cognizable danger of recurrent violation."

Accordingly, FDA's motion for summary judgment [Dkt. 19] and motion to dismiss counterclaims [Dkt. 20] will be granted. In addition, FDA's request for a permanent injunction will be granted.[13] Memorializing orders accompany this Memorandum Opinion.

Date: July 23, 2012

/s/
ROSEMARY M. COLLYER
United States District Judge

[13] Defendants did not assert any opposition to the specific language of FDA's proposed Order of Permanent Injunction.

FUERST ITTLEMAN DAVID & JOSEPH PL

ADDENDUM 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	)	
	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 10-cv-1327 (RMC)
	)	
REGENERATIVE SCIENCES, LLC, *et al.*,	)	
	)	
Defendants.	)	

ORDER OF PERMANENT INJUNCTION

The Court having considered Plaintiff's motion for summary judgment and supporting documents and any opposition thereto; having found that the cultured cell product is a drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g) ("FDCA") and a biological product within the meaning of 42 U.S.C. § 262; having found that Regenerative Sciences, LLC, a corporation, and Christopher J. Centeno, M.D., John R. Schultz, M.D., and Michelle R. Cheever, individuals (collectively, "Defendants") are causing the adulteration and misbranding of the cultured cell product within the meaning of 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 353(b)(4), while it is held for sale after shipment of one or more of its components in interstate commerce; and having found that the Defendants, unless restrained by order of this Court, will continue to violate the FDCA,

IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. Plaintiff's motion for summary judgment is granted.

2. This Court has jurisdiction over the subject matter and all parties to this action.

3. The Complaint states a cause of action against the Defendants under the FDCA.

4. For purposes of this Order, the term "drug" shall refer to any human cell, tissue, or cellular or tissue-based product ("HCT/P") as defined in 21 C.F.R. § 1271.3(d) that does not meet all of the criteria in 21 C.F.R. § 1271.10 or the criteria for an exception in 21 C.F.R. § 1271.15.

5. Defendants, and all of their directors, officers, agents, employees, successors, representatives, assigns, and attorneys, and any and all persons in active concert or participation with any of them, who have received actual notice of this Order by personal service or otherwise, are hereby permanently enjoined under 21 U.S.C. § 332(a) from directly or indirectly doing or causing to be done any act that:

A. Violates 21 U.S.C. § 331(k) by causing any drug within the meaning of 21 U.S.C. § 321(g) to become adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B) or to become misbranded within the meaning of 21 U.S.C. § 352(f)(1) or § 353(b)(4), while such article is held for sale after shipment of one or more of its components in interstate commerce.

B. Violates 21 U.S.C. § 331 (a) by introducing or causing to be introduced, or delivering or causing to be delivered for introduction, into interstate commerce any drug that is adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B) or misbranded within the meaning of 21 U.S.C. § 352(f)(1) or § 353(b)(4).

6. Defendants and each and all of their directors, officers, agents, employees, representatives, successors, assigns, attorneys, and any and all persons in active concert or participation with any of them, who have received actual notice of this Order by personal service

or otherwise, are permanently restrained and enjoined under 21 U.S.C. § 332(a) from directly or indirectly manufacturing, processing, packing, repacking, labeling, and distributing the cultured cell product or any other drug, unless and until:

A. Defendants' methods, facilities, and controls used to manufacture, process, pack, repack, label, hold, and distribute such products are established, operated, and administered in conformity with current good manufacturing practice, 21 U.S.C. § 351(a)(2)(B) and 21 C.F.R. Parts 210-211, 600-680, and 1271 (hereafter, "CGMP");

B. Defendants retain, at Defendants' expense, an independent person or persons (the "expert"), without personal or financial ties (other than the consulting agreement between the parties) to Defendants or their immediate families, who by reason of background, experience, education, and training, is qualified to inspect Defendants' facilities to determine whether their methods, facilities, and controls are operated and administered in conformity with CGMP and to evaluate the labeling of Defendants' cultured cell product and any other drugs manufactured, processed, packed, labeled, held, and distributed by Defendants to determine whether they are in compliance with 21 U.S.C. §§ 352(f) and 353(b)(4). Defendants shall notify FDA in writing of the identity of the expert within ten (10) days of retaining such expert;

C. The expert shall perform a comprehensive inspection of Defendants' facility at 6850 West 116th Avenue, Unit D, Broomfield, Colorado and any other location at which Defendants manufacture, process, pack, repack, label, hold, or distribute the cultured cell product or any other drug, and the methods and controls used to manufacture, process, package, repackage, label, hold, and distribute such products to determine whether such facilities,

methods, and controls are, at a minimum, in conformity with CGMP, and to determine whether the labeling of Defendants' cultured cell product and any other drugs manufactured, processed, packed, labeled, held, and distributed by Defendants is in compliance with 21 U.S.C. §§ 352(f) and 353(b)(4);

D. The expert certifies to FDA that:

(1) The expert has inspected Defendants' facilities, methods, and controls and product labeling;

(2) All deviations from CGMP brought to Defendants' attention by FDA, the expert, or any other source have been corrected; and

(3) Such facilities, methods, processes, and controls are in compliance with CGMP and the labeling of Defendants' cultured cell product and any other drugs manufactured, processed, packed, labeled, held, and distributed by Defendants is in compliance with 21 U.S.C. §§ 352(f) and 353(b)(4). As part of this certification, the expert shall include a detailed and complete report of the results of the expert's inspections. The expert shall submit his report(s) to FDA at the address(es) specified in paragraph 19.

E. Defendants ensure that the labeling for all of the cultured cell products and any other drugs that they manufacture, process, pack, repack, label, hold, and distribute bear adequate directions for use within the meaning of 21 U.S.C. § 352(f)(1) and all applicable regulations, or are in full compliance with a regulatory exemption to 21 U.S.C. § 352(f)(1) in 21 C.F.R. Part 201 Subpart D;

F. Defendants ensure that, at all times prior to dispensing, the labels for the cultured cell products and any other prescription drugs within the meaning of 21 U.S.C. § 353(b) that they manufacture, process, pack, repack, label, hold, and distribute bear the symbol "Rx only" pursuant to 21 U.S.C. § 353(b)(4)(A);

G. Defendants report to FDA in writing the actions they have taken to:

(1) Correct the CGMP deviations brought to Defendants' attention by FDA, the CGMP expert, and any other source;

(2) Ensure that the methods used in, and the facilities and controls used for, manufacturing, processing, packing, repacking, labeling, holding, and distributing are operated and will be continuously administered in conformity with CGMP; and

(3) Ensure that their cultured cell products and any other drugs that Defendants manufacture, process, pack, repack, or label are not misbranded within the meaning of 21 U.S.C. §§ 352(f)(1) and 353(b)(4);

H. FDA representatives inspect Defendants' facilities to determine whether the requirements of this Order have been met, and whether those facilities are otherwise operated in conformity with CGMP and any drugs that they manufacture, process, pack, repack, or label are labeled in conformity with 21 U.S.C. §§ 352(f)(1) and 353(b)(4); and

I. FDA notifies Defendants in writing that Defendants appear to be in compliance with the requirements set forth in paragraphs 6.A.-H.

7. If Defendants manufacture, process, pack, repack, label, hold, or distribute any HCT/P that meets all of the criteria in 21 C.F.R. § 1271.10, Defendants shall continuously ensure that the HCT/P and Defendants' establishment comply will all of the requirements in Part 1271.

8. If, at any time after entry of this Order, FDA determines, based on the results of an inspection, the analysis of samples, a report or data prepared or submitted by Defendants or the expert pursuant to this Order, or any other information, that Defendants have failed to comply with any provision of this Order, or have violated the FDCA or applicable regulations, or that additional corrective actions are necessary to achieve compliance with this Order, the FDCA, or applicable regulations, FDA may, as and when it deems necessary, direct Defendants in writing to take appropriate actions. Such actions may include, but are not limited to, the following:

A. Cease manufacturing, processing, packing, repacking, labeling, holding, and distributing the cultured cell product, any other drugs, and HCT/Ps (as defined in 21 C.F.R. § 1271.3(d));

B. Recall, at Defendants' sole expense, any products that are adulterated or misbranded or are otherwise in violation of this Order, the FDCA, or applicable regulations; or

C. Take any other corrective action(s) as FDA, in its discretion, deems necessary to bring Defendants and their products into compliance with this Order, the FDCA, or applicable regulations.

9. The following process and procedures shall apply when FDA issues a directive under paragraph 8, except as provided in subparagraph D below:

A. Unless a different time frame is specified by FDA in its directive, within ten (10) business days after receiving such directive, Defendants shall notify FDA in writing either that: (1) Defendants are undertaking or have undertaken corrective action, in which event Defendants also shall describe the specific action taken or proposed to be taken and the proposed schedule for completing the action; or (2) Defendants do not agree with FDA's directive. If Defendants notify FDA that they do not agree with FDA's directive, Defendants shall explain in writing the basis for their disagreement; in so doing, Defendants also may propose specific alternative actions and specific time frames for achieving FDA's objectives.

B. If Defendants notify FDA that they do not agree with FDA's directive, FDA will review Defendants' notification and thereafter, in writing, affirm, modify, or withdraw its directive, as the agency deems appropriate. If FDA affirms or modifies its directive, it shall explain the basis for its decision in writing. The written notice of affirmation or modification shall constitute final agency action.

C. If FDA affirms or modifies its directive, Defendants shall, upon receipt of FDA's directive, immediately implement the directive (as modified, if applicable), and if they so choose, bring the matter before this Court on an expedited basis. Defendants shall continue to diligently implement FDA's directive while the matter is before the Court and unless and until the Court sets aside, stays, reverses, vacates, or modifies FDA's directive. Any review of FDA's decision under this paragraph shall be made in accordance with the terms set forth in paragraph 17 of this Order.

D. The process and procedures set forth in paragraph 9.A.-C. shall not apply to any directive issued pursuant to paragraph 8 if it states that, in FDA's judgment, the matter raises significant public health concerns. In such case, Defendants shall, upon receipt of such a directive, immediately and fully comply with the terms of that directive. Should the Defendants seek to challenge any such directive, they may petition this Court for relief.

10. Representatives of FDA shall be permitted, without prior notice and as and when FDA deems necessary, to inspect Defendants' places of business and take any other measures necessary to monitor and ensure continuing compliance with this Order. During inspections, FDA representatives shall be permitted to: have immediate access to buildings, equipment, in-process or unfinished and finished materials, containers, packaging material, labeling, and other promotional material therein; take photographs and make video recordings; take samples of Defendants' in-process or unfinished and finished materials, containers, packaging material, labeling, and other promotional material; and examine and copy all records relating to the manufacture, processing, packing, repacking, labeling, holding, and distribution of any and all cultured cell products, drugs, HCT/Ps, and their components. The inspections shall be permitted upon presentation of a copy of this Order and appropriate credentials. The inspection authority granted by this Order is separate from, and in addition to, the authority to make inspections under the FDCA, 21 U.S.C. § 374.

11. Defendants shall reimburse FDA for the costs of all FDA inspections, investigations, supervision, reviews, examinations, and analyses specified in this Order or that FDA deems necessary to evaluate Defendants' compliance with this Order. The costs of such

inspections shall be borne by Defendants at the prevailing rates in effect at the time the costs are incurred. As of the date of this Order, these rates are: $85.49 per hour and fraction thereof per representative for inspection work; $102.49 per hour or fraction thereof per representative for analytical or review work; $.55 per mile for travel expenses by automobile; government rate or the equivalent for travel by air or other means; and the published government per diem rate or the equivalent for the areas in which the inspections are performed per-day, per-representative for subsistence expenses, where necessary. In the event that the standard rates applicable to FDA supervision of court-ordered compliance are modified, these rates shall be increased or decreased without further order of the Court.

12. This Order does not apply to drugs that are both (A) the subject of an effective new drug application or biologics license application approved by FDA and (B) not manufactured, processed, packed, or labeled by Defendants.

13. Defendants shall immediately post a copy of this Order in a common area at Defendants' facility and at any other location at which Defendants conduct business and shall ensure that the Order remains posted for no less than twelve (12) months.

14. Within ten (10) calendar days after the entry of this Order, Defendants shall provide a copy of this Order, by personal service or registered mail, to each and all of their directors, officers, agents, employees, representatives, successors, assigns, attorneys, and any and all persons in active concert or participation with any of them (collectively referred to as "Associated Persons"). Within thirty (30) calendar days of the date of entry of this Order, Defendants shall provide to FDA an affidavit of compliance, signed by a person with personal

knowledge of the facts, stating the fact and manner of compliance with the provisions of this paragraph and identifying the names, addresses, and positions of all persons who have received a copy of this Order.

15. In the event that any of the Defendants becomes associated with any additional Associated Person(s) at any time after entry of this Order, Defendants immediately shall provide a copy of this Order, by personal service or certified mail (restricted delivery, return receipt requested), to such Associated Person(s). Within thirty (30) calendar days of each time any of the Defendants becomes associated with any such additional Associated Person(s), Defendants shall provide to FDA an affidavit stating the fact and manner of their compliance with this paragraph, identifying the names, addresses, and positions of all Associated Persons who received a copy of this Order pursuant to this paragraph, and attaching a copy of the executed certified mail return receipts. Within ten (10) calendar days of receiving a request from FDA for any information or documentation that FDA deems necessary to evaluate Defendants' compliance with this paragraph, Defendants shall provide such information or documentation to FDA.

16. Defendants shall notify FDA at least fifteen (15) calendar days before any change in ownership, character, or name of their businesses, including incorporation, reorganization, bankruptcy, assignment, or sale resulting in the emergence of a successor business or corporation, the creation or dissolution of subsidiaries, or any other change in the corporate structure or identity of Regenerative Sciences, LLC or in the sale or assignment of any business assets, such as buildings, equipment, or inventory, that may affect obligations arising out of this

Order. Defendants shall provide a copy of this Order to any potential successor or assign at least fifteen (15) calendar days before any sale or assignment. Defendants shall furnish FDA with an affidavit of compliance with this paragraph no later than ten (10) calendar days prior to such assignment or change in ownership.

17. Defendants shall abide by the decisions of FDA, and FDA's decisions shall be final. All decisions conferred upon FDA in this Order shall be vested in FDA's discretion and, if contested, shall be reviewed by this Court under the arbitrary and capricious standard set forth in 5 U.S.C. § 706(2)(A). Review by the Court of any FDA decision rendered pursuant to this Order shall be based exclusively on the written record before FDA at the time of the decision. No discovery shall be taken by either party.

18. Should the United States of America bring, and prevail in, a contempt action to enforce the terms of this Order, Defendants shall, in addition to other remedies, reimburse the United States for its attorneys' fees (including overhead), travel expenses incurred by attorneys and witnesses, court costs, expert witness fees, and investigational and analytical expenses incurred in bringing such action.

19. All notifications, certifications, reports, correspondence, and other communications to FDA required by the terms of this Order shall be addressed to the Director, FDA Denver District Office, 6th & Kipling St, Building 20, Denver Federal Center, Denver, CO 80225-0087 and to the Director, Office of Compliance and Biologics Quality, CBER, 1401 Rockville Pike, Suite 200 N, Rockville, MD 20852-1448.

20. This Court retains jurisdiction of this action and the parties thereto for the purpose of enforcing and modifying this Order and for the purpose of granting such additional relief as may be necessary or appropriate.

IT IS SO ORDERED, this 23rd day of July, 2012.

/s/
ROSEMARY M. COLLYER
United States District Judge

FUERST ITTLEMAN DAVID & JOSEPH PL

ADDENDUM 3

Subsec. (i)(1)(C). Pub. L. 105–248, §11, inserted ''(or of an accreditation body approved pursuant to subsection (e) of this section)'' after ''of the Secretary'' and inserted ''(or such accreditation body or State carrying out certification program requirements pursuant to subsection (q) of this section)'' after ''that the Secretary''.

Subsec. (i)(1)(D). Pub. L. 105–248, §9(3), inserted ''or local'' after ''any State'' and ''or local agency'' after ''by the State''.

Subsec. (i)(2)(A). Pub. L. 105–248, §12, substituted ''has reason to believe that the circumstance of the case will support one or more of the findings described in paragraph (1) and that—'' and cls. (i) and (ii) for ''makes the finding described in paragraph (1) and determines that—

''(i) the failure of a facility to comply with the standards established by the Secretary under subsection (f) of this section presents a serious risk to human health; or

''(ii) a facility has engaged in an action described in subparagraph (D) or (E) of paragraph (1).''

Subsec. (q)(4)(B). Pub. L. 105–248, §13, substituted ''certified'' for ''accredited''.

Subsec. (r)(2)(A). Pub. L. 105–248, §2, substituted ''subsection (p)'' for ''subsection (q)'' and ''2002'' for ''1997''.

Subsec. (r)(2)(B). Pub. L. 105–248, §2, substituted ''fiscal years'' for ''fiscal year'' and ''2002'' for ''1997''.

CHANGE OF NAME

Committee on Labor and Human Resources of Senate changed to Committee on Health, Education, Labor, and Pensions of Senate by Senate Resolution No. 20, One Hundred Sixth Congress, Jan. 19, 1999.

Committee on Energy and Commerce of House of Representatives treated as referring to Committee on Commerce of House of Representatives by section 1(a) of Pub. L. 104–14, set out as a note preceding section 21 of Title 2, The Congress. Committee on Commerce of House of Representatives changed to Committee on Energy and Commerce of House of Representatives, and jurisdiction over matters relating to securities and exchanges and insurance generally transferred to Committee on Financial Services of House of Representatives by House Resolution No. 5, One Hundred Seventh Congress, Jan. 3, 2001.

TERMINATION OF ADVISORY COMMITTEES

Advisory committees established after Jan. 5, 1973, to terminate not later than the expiration of the 2-year period beginning on the date of their establishment, unless, in the case of a committee established by the President or an officer of the Federal Government, such committee is renewed by appropriate action prior to the expiration of such 2-year period, or in the case of a committee established by Congress, its duration is otherwise provided for by law. See section 14 of Pub. L. 92–463, Oct. 6, 1972, 86 Stat. 776, set out in the Appendix to Title 5, Government Organization and Employees.

Pub. L. 93–641, §6, Jan. 4, 1975, 88 Stat. 2275, set out as a note under section 217a of this title, provided that an advisory committee established pursuant to the Public Health Service Act shall terminate at such time as may be specifically prescribed by an Act of Congress enacted after Jan. 4, 1975.

REGULATIONS

Pub. L. 103–183, title VII, §707, Dec. 14, 1993, 107 Stat. 2241, provided that: ''The Secretary of Health and Human Services is authorized to issue interim final regulations—

''(1) under which the Secretary may approve accreditation bodies under section 354(e) of the Public Health Service Act (42 U.S.C. 263b(e)); and

''(2) establishing quality standards under section 354(f) of the Public Health Service Act (42 U.S.C. 263b(f)).''

STUDY

Section 3 of Pub. L. 102–539 directed Comptroller General of United States to conduct a study of the certification program authorized by this section to determine if the program has resulted in improvement of quality and accessibility of mammography services, and if the program has reduced the frequency of poor quality mammography and improved early detection of breast cancer, with Comptroller General, not later than 3 years from Oct. 27, 1992, submit to Congress an interim report of results of study and, not later than 5 years from such date to submit a final report.

PART G—QUARANTINE AND INSPECTION

§ 264. Regulations to control communicable diseases

(a) Promulgation and enforcement by Surgeon General

The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary.

(b) Apprehension, detention, or conditional release of individuals

Regulations prescribed under this section shall not provide for the apprehension, detention, or conditional release of individuals except for the purpose of preventing the introduction, transmission, or spread of such communicable diseases as may be specified from time to time in Executive orders of the President upon the recommendation of the Secretary, in consultation with the Surgeon General,[1].

(c) Application of regulations to persons entering from foreign countries

Except as provided in subsection (d) of this section, regulations prescribed under this section, insofar as they provide for the apprehension, detention, examination, or conditional release of individuals, shall be applicable only to individuals coming into a State or possession from a foreign country or a possession.

(d) Apprehension and examination of persons reasonably believed to be infected

(1) Regulations prescribed under this section may provide for the apprehension and examination of any individual reasonably believed to be infected with a communicable disease in a qualifying stage and (A) to be moving or about to move from a State to another State; or (B) to be a probable source of infection to individuals who, while infected with such disease in a qualifying stage, will be moving from a State to another State. Such regulations may provide that if upon examination any such individual is found to be infected, he may be detained for such time and in such manner as may be reason-

[1] So in original. Comma probably should not appear.

ably necessary. For purposes of this subsection, the term ''State'' includes, in addition to the several States, only the District of Columbia.

(2) For purposes of this subsection, the term ''qualifying stage'', with respect to a communicable disease, means that such disease—

(A) is in a communicable stage; or

(B) is in a precommunicable stage, if the disease would be likely to cause a public health emergency if transmitted to other individuals.

(e) Preemption

Nothing in this section or section 266 of this title, or the regulations promulgated under such sections, may be construed as superseding any provision under State law (including regulations and including provisions established by political subdivisions of States), except to the extent that such a provision conflicts with an exercise of Federal authority under this section or section 266 of this title.

(July 1, 1944, ch. 373, title III, § 361, 58 Stat. 703; 1953 Reorg. Plan No. 1, §§ 5, 8, eff. Apr. 11, 1953, 18 F.R. 2053, 67 Stat. 631; Pub. L. 86–624, § 29(c), July 12, 1960, 74 Stat. 419; Pub. L. 94–317, title III, § 301(b)(1), June 23, 1976, 90 Stat. 707; Pub. L. 107–188, title I, § 142(a)(1), (2), (b)(1), (c), June 12, 2002, 116 Stat. 626, 627.)

AMENDMENTS

2002—Pub. L. 107–188, § 142(a)(1), (2), (b)(1), and (c), which directed certain amendments to section 361 of the Public Health Act, was executed by making the amendments to this section, which is section 361 of the Public Health Service Act, to reflect the probable intent of Congress. See below.

Subsec. (b). Pub. L. 107–188, § 142(a)(1), substituted ''Executive orders of the President upon the recommendation of the Secretary, in consultation with the Surgeon General,'' for ''Executive orders of the President upon the recommendation of the National Advisory Health Council and the Surgeon General''.

Subsec. (d). Pub. L. 107–188, § 142(a)(2), (b)(1), substituted in first sentence ''Regulations'' for ''On recommendation of the National Advisory Health Council, regulations'', ''in a qualifying stage'' for ''in a communicable stage'' in two places, designated existing text as par. (1) and substituted ''(A)'' and ''(B)'' for ''(1)'' and ''(2)'', respectively, and added par. (2).

Subsec. (e). Pub. L. 107–188, § 142(c), added subsec. (e).

1976—Subsec. (d). Pub. L. 94–317 inserted provision defining ''State'' to include, in addition to the several States, only the District of Columbia.

1960—Subsec. (c). Pub. L. 86–624 struck out reference to Territory of Hawaii.

EFFECTIVE DATE OF 1960 AMENDMENT

Amendment by Pub. L. 86–624 effective Aug. 21, 1959, see section 47(f) of Pub. L. 86–624, set out as a note under section 201 of this title.

TRANSFER OF FUNCTIONS

Office of Surgeon General abolished by section 3 of Reorg. Plan No. 3 of 1966, eff. June 25, 1966, 31 F.R. 8855, 80 Stat. 1610, and functions thereof transferred to Secretary of Health, Education, and Welfare by section 1 of Reorg. Plan No. 3 of 1966, set out as a note under section 202 of this title. Secretary of Health, Education, and Welfare redesignated Secretary of Health and Human Services by section 509(b) of Pub. L. 96–88 which is classified to section 3508(b) of Title 20, Education.

Functions of Federal Security Administrator transferred to Secretary of Health, Education, and Welfare and all agencies of Federal Security Agency transferred to Department of Health, Education, and Welfare by section 5 of Reorg. Plan No. 1 of 1953, set out as a note under section 3501 of this title. Federal Security Agency and office of Administrator abolished by section 8 of Reorg. Plan No. 1 of 1953. Secretary and Department of Health, Education, and Welfare redesignated Secretary and Department of Health and Human Services by section 509(b) of Pub. L. 96–88 which is classified to section 3508(b) of Title 20.

EVALUATION OF PUBLIC HEALTH AUTHORITIES

Pub. L. 110–392, title I, § 121, Oct. 13, 2008, 122 Stat. 4200, provided that:

''(a) IN GENERAL.—Not later than 180 days after the date of enactment of the Comprehensive Tuberculosis Elimination Act of 2008 [Oct. 13, 2008], the Secretary of Health and Human Services shall prepare and submit to the appropriate committees of Congress a report that evaluates and provides recommendations on changes needed to Federal and State public health authorities to address current disease containment challenges such as isolation and quarantine.

''(b) CONTENTS OF EVALUATION.—The report described in subsection (a) shall include—

''(1) an evaluation of the effectiveness of current policies to detain patients with active tuberculosis;

''(2) an evaluation of whether Federal laws should be strengthened to expressly address the movement of individuals with active tuberculosis; and

''(3) specific legislative recommendations for changes to Federal laws, if any.

''(c) UPDATE OF QUARANTINE REGULATIONS.—Not later than 240 days after the date of enactment of this Act [Oct. 13, 2008], the Secretary of Health and Human Services shall promulgate regulations to update the current interstate and foreign quarantine regulations found in parts 70 and 71 of title 42, Code of Federal Regulations.''

EXECUTIVE ORDER NO. 12452

Ex. Ord. No. 12452, Dec. 22, 1983, 48 F.R. 56927, which specified certain communicable diseases for regulations providing for the apprehension, detention, or conditional release of individuals to prevent the introduction, transmission, or spread of such diseases, was revoked by Ex. Ord. No. 13295, § 5, Apr. 4, 2003, 68 F.R. 17255, set out below.

EX. ORD. NO. 13295. REVISED LIST OF QUARANTINABLE COMMUNICABLE DISEASES

Ex. Ord. No. 13295, Apr. 4, 2003, 68 F.R. 17255, as amended by Ex. Ord. No. 13375, § 1, Apr. 1, 2005, 70 F.R. 17299, provided:

By the authority vested in me as President by the Constitution and the laws of the United States of America, including section 361(b) of the Public Health Service Act (42 U.S.C. 264(b)), it is hereby ordered as follows:

SECTION 1. Based upon the recommendation of the Secretary of Health and Human Services (the ''Secretary''), in consultation with the Surgeon General, and for the purpose of specifying certain communicable diseases for regulations providing for the apprehension, detention, or conditional release of individuals to prevent the introduction, transmission, or spread of suspected communicable diseases, the following communicable diseases are hereby specified pursuant to section 361(b) of the Public Health Service Act:

(a) Cholera; Diphtheria; infectious Tuberculosis; Plague; Smallpox; Yellow Fever; and Viral Hemorrhagic Fevers (Lassa, Marburg, Ebola, Crimean-Congo, South American, and others not yet isolated or named).

(b) Severe Acute Respiratory Syndrome (SARS), which is a disease associated with fever and signs and symptoms of pneumonia or other respiratory illness, is transmitted from person to person predominantly by the aerosolized or droplet route, and, if spread in the population, would have severe public health consequences.

(c) Influenza caused by novel or reemergent influenza viruses that are causing, or have the potential to cause, a pandemic.

SEC. 2. The Secretary, in the Secretary's discretion, shall determine whether a particular condition constitutes a communicable disease of the type specified in section 1 of this order.

SEC. 3. The functions of the President under sections 362 and 364(a) of the Public Health Service Act (42 U.S.C. 265 and 267(a)) are assigned to the Secretary.

SEC. 4. This order is not intended to, and does not, create any right or benefit enforceable at law or equity by any party against the United States, its departments, agencies, entities, officers, employees or agents, or any other person.

SEC. 5. Executive Order 12452 of December 22, 1983, is hereby revoked.

GEORGE W. BUSH.

§ 265. Suspension of entries and imports from designated places to prevent spread of communicable diseases

Whenever the Surgeon General determines that by reason of the existence of any communicable disease in a foreign country there is serious danger of the introduction of such disease into the United States, and that this danger is so increased by the introduction of persons or property from such country that a suspension of the right to introduce such persons and property is required in the interest of the public health, the Surgeon General, in accordance with regulations approved by the President, shall have the power to prohibit, in whole or in part, the introduction of persons and property from such countries or places as he shall designate in order to avert such danger, and for such period of time as he may deem necessary for such purpose.

(July 1, 1944, ch. 373, title III, § 362, 58 Stat. 704.)

TRANSFER OF FUNCTIONS

Office of Surgeon General abolished by section 3 of Reorg. Plan No. 3 of 1966, eff. June 25, 1966, 31 F.R. 8855, 80 Stat. 1610, and functions thereof transferred to Secretary of Health, Education, and Welfare by section 1 of Reorg. Plan No. 3 of 1966, set out as a note under section 202 of this title. Secretary of Health, Education, and Welfare redesignated Secretary of Health and Human Services by section 509(b) of Pub. L. 96–88 which is classified to section 3508(b) of Title 20, Education.

DELEGATION OF FUNCTIONS

For assignment of functions of President under this section, see section 3 of Ex. Ord. No. 13295, Apr. 4, 2003, 68 F.R. 17255, set out as a note under section 264 of this title.

§ 266. Special quarantine powers in time of war

To protect the military and naval forces and war workers of the United States, in time of war, against any communicable disease specified in Executive orders as provided in subsection (b) of section 264 of this title, the Secretary, in consultation with the Surgeon General, is authorized to provide by regulations for the apprehension and examination, in time of war, of any individual reasonably believed (1) to be infected with such disease and (2) to be a probable source of infection to members of the armed forces of the United States or to individuals engaged in the production or transportation of arms, munitions, ships, food, clothing, or other supplies for the armed forces. Such regulations may provide that if upon examination any such individual is found to be so infected, he may be detained for such time and in such manner as may be reasonably necessary.

(July 1, 1944, ch. 373, title III, § 363, 58 Stat. 704; Pub. L. 107–188, title I, § 142(a)(3), (b)(2), June 12, 2002, 116 Stat. 626, 627.)

AMENDMENTS

2002—Pub. L. 107–188, which directed substitution of ''the Secretary, in consultation with the Surgeon General,'' for ''the Surgeon General, on recommendation of the National Advisory Health Council,'' and striking out of ''in a communicable stage'' after ''(1) to be infected with such disease'', in section 363 of the Public Health Act, was executed to this section, which is section 363 of the Public Health Service Act, to reflect the probable intent of Congress.

TRANSFER OF FUNCTIONS

Office of Surgeon General abolished by section 3 of Reorg. Plan No. 3 of 1966, eff. June 25, 1966, 31 F.R. 8855, 80 Stat. 1610, and functions thereof transferred to Secretary of Health, Education, and Welfare by section 1 of Reorg. Plan No. 3 of 1966, set out as a note under section 202 of this title. Secretary of Health, Education, and Welfare redesignated Secretary of Health and Human Services by section 509(b) of Pub. L. 96–88 which is classified to section 3508(b) of Title 20, Education.

TERMINATION OF WAR AND EMERGENCIES

Joint Res. July 25, 1947, ch. 327, § 3, 61 Stat. 451, provided that in the interpretation of this section, the date July 25, 1947, shall be deemed to be the date of termination of any state of war theretofore declared by Congress and of the national emergencies proclaimed by the President on Sept. 8, 1939, and May 27, 1941.

§ 267. Quarantine stations, grounds, and anchorages

(a) Control and management

Except as provided in title II of the Act of June 15, 1917, as amended [50 U.S.C. 191 et seq.], the Surgeon General shall control, direct, and manage all United States quarantine stations, grounds, and anchorages, designate their boundaries, and designate the quarantine officers to be in charge thereof. With the approval of the President he shall from time to time select suitable sites for and establish such additional stations, grounds, and anchorages in the States and possessions of the United States as in his judgment are necessary to prevent the introduction of communicable diseases into the States and possessions of the United States.

(b) Hours of inspection

The Surgeon General shall establish the hours during which quarantine service shall be performed at each quarantine station, and, upon application by any interested party, may establish quarantine inspection during the twenty-four hours of the day, or any fraction thereof, at such quarantine stations as, in his opinion, require such extended service. He may restrict the performance of quarantine inspection to hours of daylight for such arriving vessels as cannot, in his opinion, be satisfactorily inspected during hours of darkness. No vessel shall be required to undergo quarantine inspection during the hours of darkness, unless the quarantine officer at such quarantine station shall deem an immediate inspection necessary to protect the public health. Uniformity shall not be required in the hours during which quarantine inspection may be obtained at the various ports of the United States.

FUERST ITTLEMAN DAVID & JOSEPH PL

ADDENDUM 4

AUTHORITY: 42 U.S.C. 216, 243, 263a, 264, 271.

SOURCE: 66 FR 5466, Jan. 19, 2001, unless otherwise noted.

Subpart A—General Provisions

§ 1271.1 What are the purpose and scope of this part?

(a) *Purpose.* The purpose of this part, in conjunction with §§ 207.20(f), 210.1(c), 210.2, 807.20(d), and 820.1(a) of this chapter, is to create a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/P's) and to establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's.

(b) *Scope.* (1) If you are an establishment that manufactures HCT/P's that are regulated solely under the authority of section 361 of the Public Health Service Act (the PHS Act), this part requires you to register and list your HCT/P's with the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research and to comply with the other requirements contained in this part, whether or not the HCT/P enters into interstate commerce. Those HCT/P's that are regulated solely under the authority of section 361 of the PHS Act are described in § 1271.10.

(2) If you are an establishment that manufactures HCT/P's that are regulated as drugs, devices and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act, §§ 207.20(f) and 807.20(d) of this chapter require you to register and list your HCT/P's following the procedures in subpart B of this part. Sections 210.1(c), 210.2, 211.1(b), and 820.1(a) of this chapter require you to comply with the donor-eligibility procedures in subpart C of this part and the current good tissue practice procedures in subpart D of this part, in addition to all other applicable regulations.

[66 FR 5466, Jan. 19, 2001, as amended at 69 FR 29829, May 25, 2004]

§ 1271.3 How does FDA define important terms in this part?

The following definitions apply only to this part:

(a) *Autologous use* means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.

(b) *Establishment* means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products. ''Establishment'' includes:

(1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of

human cells, tissues, and cellular and tissue-based products; and

(2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products.

(c) *Homologous use* means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

(d) *Human cells, tissues, or cellular or tissue-based products (HCT/Ps)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;

(4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

(5) Ancillary products used in the manufacture of HCT/P;

(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in §809.3(a) of this chapter.

(8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled ''For use in organ transplantation only.''

(e) *Manufacture means*, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

(f) *Minimal manipulation* means:

(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

(2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

(g) *Transfer* means the placement of human reproductive cells or tissues into a human recipient.

(h) *Biohazard legend* appears on the label as follows and is used to mark HCT/Ps that present a known or suspected relevant communicable disease risk.

BIOHAZARD

(i) *Blood component* means a product containing a part of human blood separated by physical or mechanical means.

(j) *Colloid* means:

(1) A protein or polysaccharide solution, such as albumin, dextran, or hetastarch, that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment; or

(2) Blood components such as plasma and platelets.

(k) *Crystalloid* means an isotonic salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer's lactate solution, or 5 percent dextrose in water.

(l) *Directed reproductive donor* means a donor of reproductive cells or tissue (including semen, oocytes, and embryos to which the donor contributed

the spermatozoa or oocyte) to a specific recipient, and who knows and is known by the recipient before donation. The term directed reproductive donor does not include a sexually intimate partner under §1271.90.

(m) *Donor* means a person, living or dead, who is the source of cells or tissue for an HCT/P.

(n) *Donor medical history interview means* a documented dialog about the donor's medical history and relevant social behavior, including activities, behaviors, and descriptions considered to increase the donor's relevant communicable disease risk:

(1) With the donor, if the donor is living and able to participate in the interview, or

(2) If not, with an individual or individuals able to provide the information sought in the interview (e.g., the donor's next-of-kin, the nearest available relative, a member of the donor's household, an individual with an affinity relationship, and/or the primary treating physician).

(o) *Physical assessment of a cadaveric donor* means a limited autopsy or recent antemortem or postmortem physical examination of the donor to assess for signs of a relevant communicable disease and for signs suggestive of any risk factor for a relevant communicable disease.

(p) *Plasma dilution* means a decrease in the concentration of the donor's plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids.

(q) *Quarantine* means the storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation.

(r) *Relevant communicable disease agent or disease* means:

(1)(i) For all human cells and tissues, a communicable disease or disease agent listed as follows:

(A) Human immunodeficiency virus, types 1 and 2;

(B) Hepatitis B virus;

(C) Hepatitis C virus;

(D) Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease; and

(E) *Treponema pallidum*.

(ii) For viable, leukocyte-rich cells and tissues, a cell-associated disease agent or disease listed as follows:

(A) Human T-lymphotropic virus, type I; and

(B) Human T-lymphotropic virus, type II.

(iii) For reproductive cells or tissues, a disease agent or disease of the genitourinary tract listed as follows:

(A) *Chlamydia trachomatis*; and

(B) *Neisseria gonorrhea*.

(2) A disease agent or disease not listed in paragraph (r)(1) of this section:

(i) For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with it, such as medical personnel, because the disease agent or disease:

(A) Is potentially transmissible by an HCT/P and

(B) Either of the following applies:

(*1*) The disease agent or disease has sufficient incidence and/or prevalence to affect the potential donor population, or

(*2*) The disease agent or disease may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection;

(ii) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and

(iii) For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available.

(s) *Relevant medical records* means a collection of documents that includes a current donor medical history interview; a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and, if available, the following:

(1) Laboratory test results (other than results of testing for relevant communicable disease agents required under this subpart);

(2) Medical records;
(3) Coroner and autopsy reports; and
(4) Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease).

(t) *Responsible person* means a person who is authorized to perform designated functions for which he or she is trained and qualified.

(u) *Urgent medical need* means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P.

(v) *Act* means the Federal Food, Drug, and Cosmetic Act.

(w) *PHS Act* means the Public Health Service Act.

(x) *FDA* means the Food and Drug Administration.

(y) *Adverse reaction* means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.

(z) *Available for distribution* means that the HCT/P has been determined to meet all release criteria.

(aa) *Complaint* means any written, oral, or electronic communication about a distributed HCT/P that alleges:
(1) That an HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P; or
(2) Any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with current good tissue practice.

(bb) *Distribution* means any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor.

(cc) *Establish and maintain* means define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis.

(dd) *HCT/P deviation* means an event:
(1) That represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or
(2) That is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

(ee) *Importer of record* means the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

(ff) *Processing* means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

(gg) *Quality audit* means a documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(hh) *Quality program* means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with this part. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

(ii) *Recovery* means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

(jj) *Storage* means holding HCT/Ps for future processing and/or distribution.

(kk) *Validation* means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or *process validation*, means establishing by objective evidence that a process consistently

produces a result or HCT/P meeting its predetermined specifications.

(ll) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

[66 FR 5466, Jan. 19, 2001, as amended at 68 FR 3826, Jan. 27, 2004; 69 FR 29829, May 25, 2004; 69 FR 68680, Nov. 24, 2004]

§ 1271.10 Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(*a*) Is for autologous use;

(*b*) Is for allogeneic use in a first-degree or second-degree blood relative; or

(*c*) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.

[66 FR 5466, Jan. 19, 2001, as amended at 69 FR 68681, Nov. 24, 2004]

§ 1271.15 Are there any exceptions from the requirements of this part?

(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

(e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.

§ 1271.20 If my HCT/P's do not meet the criteria in § 1271.10, and I do not qualify for any of the exceptions in § 1271.15, what regulations apply?

If you are an establishment that manufactures an HCT/P that does not meet the criteria set out in §1271.10(a), and you do not qualify for any of the exceptions in §1271.15, your HCT/P will be regulated as a drug, device, and/or biological product under the act and/or section 351 of the PHS Act, and applicable regulations in title 21, chapter I.

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produces a result or HCT/P meeting its predetermined specifications.

(ll) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

[66 FR 5466, Jan. 19, 2001, as amended at 68 FR 3826, Jan. 27, 2004; 69 FR 29829, May 25, 2004; 69 FR 68680, Nov. 24, 2004]

§ 1271.10 Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(*a*) Is for autologous use;

(*b*) Is for allogeneic use in a first-degree or second-degree blood relative; or

(*c*) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.

[66 FR 5466, Jan. 19, 2001, as amended at 69 FR 68681, Nov. 24, 2004]

§ 1271.15 Are there any exceptions from the requirements of this part?

(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

(e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.

§ 1271.20 If my HCT/P's do not meet the criteria in § 1271.10, and I do not qualify for any of the exceptions in § 1271.15, what regulations apply?

If you are an establishment that manufactures an HCT/P that does not meet the criteria set out in §1271.10(a), and you do not qualify for any of the exceptions in §1271.15, your HCT/P will be regulated as a drug, device, and/or biological product under the act and/or section 351 of the PHS Act, and applicable regulations in title 21, chapter I.

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ADDENDUM 6

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§ 353a. Pharmacy compounding

(a) In general

Sections 351(a)(2)(B), 352(f)(1), and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding—

(1) is by—

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician,

on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between—

(i) the licensed pharmacist or licensed physician; and

(ii)(I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

(b) Compounded drug

(1) Licensed pharmacist and licensed physician

A drug product may be compounded under subsection (a) of this section if the licensed pharmacist or licensed physician—

(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—

(i) that—

(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) of this section;

(ii) that are manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and

(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

(2) Definition

For purposes of paragraph (1)(D), the term ''essentially a copy of a commercially available drug product'' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

(3) Drug product

A drug product may be compounded under subsection (a) only if—

(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

(B) such drug product is compounded in a State—

(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

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(c) Advertising and promotion

A drug may be compounded under subsection (a) of this section only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

(d) Regulations

(1) In general

The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A) of this section, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

(2) Limiting compounding

The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) of this section for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

(e) Application

This section shall not apply to—

(1) compounded positron emission tomography drugs as defined in section 321(ii) of this title; or

(2) radiopharmaceuticals.

(f) "Compounding" defined

As used in this section, the term ''compounding'' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

(June 25, 1938, ch. 675, § 503A, as added Pub. L. 105–115, title I, § 127(a), Nov. 21, 1997, 111 Stat. 2328.)

EFFECTIVE DATE

Section 127(b) of Pub. L. 105–115 provided that: ''Section 503A of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 353a], added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act [Nov. 21, 1997].''

§ 353b. Prereview of television advertisements

(a) In general

The Secretary may require the submission of any television advertisement for a drug (including any script, story board, rough, or a completed video production of the television advertisement) to the Secretary for review under this section not later than 45 days before dissemination of the television advertisement.

(b) Review

In conducting a review of a television advertisement under this section, the Secretary may make recommendations with respect to information included in the label of the drug—

(1) on changes that are—

(A) necessary to protect the consumer good and well-being; or

(B) consistent with prescribing information for the product under review; and

(2) if appropriate and if information exists, on statements for inclusion in the advertisement to address the specific efficacy of the drug as it relates to specific population groups, including elderly populations, children, and racial and ethnic minorities.

(c) No authority to require changes

Except as provided by subsection (e), this section does not authorize the Secretary to make or direct changes in any material submitted pursuant to subsection (a).

(d) Elderly populations, children, racially and ethnically diverse communities

In formulating recommendations under subsection (b), the Secretary shall take into consideration the impact of the advertised drug on elderly populations, children, and racially and ethnically diverse communities.

(e) Specific disclosures

(1) Serious risk; safety protocol

In conducting a review of a television advertisement under this section, if the Secretary determines that the advertisement would be false or misleading without a specific disclosure about a serious risk listed in the labeling of the drug involved, the Secretary may require inclusion of such disclosure in the advertisement.

(2) Date of approval

In conducting a review of a television advertisement under this section, the Secretary may require the advertisement to include, for a period not to exceed 2 years from the date of the approval of the drug under section 355 of this title or section 262 of title 42, a specific disclosure of such date of approval if the Secretary determines that the advertisement would otherwise be false or misleading.

(f) Rule of construction

Nothing in this section may be construed as having any effect on requirements under section 352(n) of this title or on the authority of the Secretary under section 314.550, 314.640, 601.45, or 601.94 of title 21, Code of Federal Regulations (or successor regulations).

(June 25, 1938, ch. 675, § 503B, as added Pub. L. 110–85, title IX, § 901(d)(2), Sept. 27, 2007, 121 Stat. 939.)

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ADDENDUM 7

Codification

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Executive Order 12612--Federalism

Source: The provisions of Executive Order 12612 of Oct. 26, 1987, appear at 52 FR 41685, 3 CFR, 1987 Comp., p. 252, unless otherwise noted.

By the authority vested in me as President by the Constitution and laws of the United States of America, and in order to restore the division of governmental responsibilities between the national government and the States that was intended by the Framers of the Constitution and to ensure that the principles of federalism established by the Framers guide the Executive departments and agencies in the formulation and implementation of policies, it is hereby ordered as follows:

Section 1. *Definitions.* For purposes of this Order:
(a) "Policies that have federalism implications" refers to regulations, legislative comments or proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.
(b) "State" or "States" refer to the States of the United States of America, individually or collectively, and, where relevant, to State governments, including units of local government and other political subdivisions established by the States.

Sec. 2. *Fundamental Federalism Principles.* In formulating and implementing policies that have federalism implications, Executive departments and agencies shall be guided by the following fundamental federalism principles:
(a) Federalism is rooted in the knowledge that our political liberties are best assured by limiting the size and scope of the national government.
(b) The people of the States created the national government when they delegated to it those enumerated governmental powers relating to matters beyond the competence of the individual States. All other sovereign powers, save those expressly prohibited the States by the Constitution, are reserved to the States or to the people.
(c) The constitutional relationship among sovereign governments, State and national, is formalized in and protected by the Tenth Amendment to the Constitution.
(d) The people of the States are free, subject only to restrictions in the Constitution itself or in constitutionally authorized Acts of Congress, to define the moral, political, and legal character of their lives.
(e) In most areas of governmental concern, the States uniquely possess the constitutional authority, the resources, and the competence to discern the sentiments of the people and to govern accordingly. In Thomas Jefferson's words, the States are "the most competent administrations for our domestic concerns and the surest bulwarks against antirepublican tendencies."
(f) The nature of our constitutional system encourages a healthy diversity in the public policies adopted by the people of the several States according to their own conditions, needs, and desires. In the search for enlightened public policy, individual States and communities are free to experiment with a variety of approaches to public issues.
(g) Acts of the national government--whether legislative, executive, or judicial in nature--that exceed the enumerated powers of that government under the Constitution violate the principle of federalism established by the Framers.
(h) Policies of the national government should recognize the responsibility of--and should encourage

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opportunities for individuals, families, neighborhoods, local governments, and private associations to achieve their personal, social, and economic objectives through cooperative effort.

(i) In the absence of clear constitutional or statutory authority, the presumption of sovereignty should rest with the individual States. Uncertainties regarding the legitimate authority of the national government should be resolved against regulation at the national level.

Sec. 3. *Federalism Policymaking Criteria.* In addition to the fundamental federalism principles set forth in section 2, Executive departments and agencies shall adhere, to the extent permitted by law, to the following criteria when formulating and implementing policies that have federalism implications:

(a) There should be strict adherence to constitutional principles. Executive departments and agencies should closely examine the constitutional and statutory authority supporting any Federal action that would limit the policymaking discretion of the States, and should carefully assess the necessity for such action. To the extent practicable, the States should be consulted before any such action is implemented. Executive Order No. 12372 ("Intergovernmental Review of Federal Programs") remains in effect for the programs and activities to which it is applicable.

(b) Federal action limiting the policymaking discretion of the States should be taken only where constitutional authority for the action is clear and certain and the national activity is necessitated by the presence of a problem of national scope. For the purposes of this Order:

(1) It is important to recognize the distinction between problems of national scope (which may justify Federal action) and problems that are merely common to the States (which will not justify Federal action because individual States, acting individually or together, can effectively deal with them).

(2) Constitutional authority for Federal action is clear and certain only when authority for the action may be found in a specific provision of the Constitution, there is no provision in the Constitution prohibiting Federal action, and the action does not encroach upon authority reserved to the States.

(c) With respect to national policies administered by the States, the national government should grant the States the maximum administrative discretion possible. Intrusive, Federal oversight of State administration is neither necessary nor desirable.

(d) When undertaking to formulate and implement policies that have federalism implications, Executive departments and agencies shall:

(1) Encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States.

(2) Refrain, to the maximum extent possible, from establishing uniform, national standards for programs and, when possible, defer to the States to establish standards.

(3) When national standards are required, consult with appropriate officials and organizations representing the States in developing those standards.

Sec. 4. *Special Requirements for Preemption.* (a) To the extent permitted by law, Executive departments and agencies shall construe, in regulations and otherwise, a Federal statute to preempt State law only when the statute contains an express preemption provision or there is some other firm and palpable evidence compelling the conclusion that the Congress intended preemption of State law, or when the exercise of State authority directly conflicts with the exercise of Federal authority under the Federal statute.

(b) Where a Federal statute does not preempt State law (as addressed in subsection (a) of this section), Executive departments and agencies shall construe any authorization in the statute for the issuance of regulations as authorizing preemption of State law by rule-making only when the statute expressly authorizes issuance of preemptive regulations or there is some other firm and palpable evidence compelling the conclusion that the Congress intended to delegate to the department or agency the authority to issue regulations preempting State law.

(c) Any regulatory preemption of State law shall be restricted to the minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.

(d) As soon as an Executive department or agency foresees the possibility of a conflict between State law and Federally protected interests within its area of regulatory responsibility, the department or agency shall consult, to the extent practicable, with appropriate officials and organizations representing the States in an effort to avoid such a conflict.

(e) When an Executive department or agency proposes to act through adjudication or rule-making to preempt State law, the department or agency shall provide all affected States notice and an opportunity for appropriate participation in the proceedings.

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Sec. 5. *Special Requirements for Legislative Proposals.* Executive departments and agencies shall not submit to the Congress legislation that would:

(a) Directly regulate the States in ways that would interfere with functions essential to the States' separate and independent existence or operate to directly displace the States' freedom to structure integral operations in areas of traditional governmental functions;

(b) Attach to Federal grants conditions that are not directly related to the purpose of the grant; or

(c) Preempt State law, unless preemption is consistent with the fundamental federalism principles set forth in section 2, and unless a clearly legitimate national purpose, consistent with the federalism policymaking criteria set forth in section 3, cannot otherwise be met.

Sec. 6. *Agency Implementation.* (a) The head of each Executive department and agency shall designate an official to be responsible for ensuring the implementation of this Order.

(b) In addition to whatever other actions the designated official may take to ensure implementation of this Order, the designated official shall determine which proposed policies have sufficient federalism implications to warrant the preparation of a Federalism Assessment. With respect to each such policy for which an affirmative determination is made, a Federalism Assessment, as described in subsection (c) of this section, shall be prepared. The department or agency head shall consider any such Assessment in all decisions involved in promulgating and implementing the policy.

(c) Each Federalism Assessment shall accompany any submission concerning the policy that is made to the Office of Management and Budget pursuant to Executive Order No. 12291 or OMB Circular No. A-19, and shall:

(1) Contain the designated official's certification that the policy has been assessed in light of the principles, criteria, and requirements stated in sections 2 through 5 of this Order;

(2) Identify any provision or element of the policy that is inconsistent with the principles, criteria, and requirements stated in sections 2 through 5 of this Order;

(3) Identify the extent to which the policy imposes additional costs or burdens on the States, including the likely source of funding for the States and the ability of the States to fulfill the purposes of the policy; and

(4) Identify the extent to which the policy would affect the States' ability to discharge traditional State governmental functions, or other aspects of State sovereignty.

Sec. 7. *Government-wide Federalism Coordination and Review.* (a) In implementing Executive Order Nos. 12291 and 12498 and OMB Circular No. A-19, the Office of Management and Budget, to the extent permitted by law and consistent with the provisions of those authorities, shall take action to ensure that the policies of the Executive departments and agencies are consistent with the principles, criteria, and requirements stated in sections 2 through 5 of this Order.

(b) In submissions to the Office of Management and Budget pursuant to Executive Order No. 12291 and OMB Circular No. A-19, Executive departments and agencies shall identify proposed regulatory and statutory provisions that have significant federalism implications and shall address any substantial federalism concerns. Where the departments or agencies deem it appropriate, substantial federalism concerns should also be addressed in notices of proposed rule-making and messages transmitting legislative proposals to the Congress.

Sec. 8. *Judicial Review.* This Order is intended only to improve the internal management of the Executive branch, and is not intended to create any right or benefit, substantive or procedural, enforceable at law by a party against the United States, its agencies, its officers, or any person.

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Federal Register
Vol. 58, No. 190
Monday, October 4, 1993

Presidential Documents

Title 3—

The President

Executive Order 12866 of September 30, 1993

Regulatory Planning and Review

The American people deserve a regulatory system that works for them, not against them: a regulatory system that protects and improves their health, safety, environment, and well-being and improves the performance of the economy without imposing unacceptable or unreasonable costs on society; regulatory policies that recognize that the private sector and private markets are the best engine for economic growth; regulatory approaches that respect the role of State, local, and tribal governments; and regulations that are effective, consistent, sensible, and understandable. We do not have such a regulatory system today.

With this Executive order, the Federal Government begins a program to reform and make more efficient the regulatory process. The objectives of this Executive order are to enhance planning and coordination with respect to both new and existing regulations; to reaffirm the primacy of Federal agencies in the regulatory decision-making process; to restore the integrity and legitimacy of regulatory review and oversight; and to make the process more accessible and open to the public. In pursuing these objectives, the regulatory process shall be conducted so as to meet applicable statutory requirements and with due regard to the discretion that has been entrusted to the Federal agencies.

Accordingly, by the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Statement of Regulatory Philosophy and Principles.*

(a) *The Regulatory Philosophy.* Federal agencies should promulgate only such regulations as are required by law, are necessary to interpret the law, or are made necessary by compelling public need, such as material failures of private markets to protect or improve the health and safety of the public, the environment, or the well-being of the American people. In deciding whether and how to regulate, agencies should assess all costs and benefits of available regulatory alternatives, including the alternative of not regulating. Costs and benefits shall be understood to include both quantifiable measures (to the fullest extent that these can be usefully estimated) and qualitative measures of costs and benefits that are difficult to quantify, but nevertheless essential to consider. Further, in choosing among alternative regulatory approaches, agencies should select those approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity), unless a statute requires another regulatory approach.

(b) *The Principles of Regulation.* To ensure that the agencies' regulatory programs are consistent with the philosophy set forth above, agencies should adhere to the following principles, to the extent permitted by law and where applicable:

(1) Each agency shall identify the problem that it intends to address (including, where applicable, the failures of private markets or public institutions that warrant new agency action) as well as assess the significance of that problem.

(2) Each agency shall examine whether existing regulations (or other law) have created, or contributed to, the problem that a new regulation is

intended to correct and whether those regulations (or other law) should be modified to achieve the intended goal of regulation more effectively.

(3) Each agency shall identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees or marketable permits, or providing information upon which choices can be made by the public.

(4) In setting regulatory priorities, each agency shall consider, to the extent reasonable, the degree and nature of the risks posed by various substances or activities within its jurisdiction.

(5) When an agency determines that a regulation is the best available method of achieving the regulatory objective, it shall design its regulations in the most cost-effective manner to achieve the regulatory objective. In doing so, each agency shall consider incentives for innovation, consistency, predictability, the costs of enforcement and compliance (to the government, regulated entities, and the public), flexibility, distributive impacts, and equity.

(6) Each agency shall assess both the costs and the benefits of the intended regulation and, recognizing that some costs and benefits are difficult to quantify, propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs.

(7) Each agency shall base its decisions on the best reasonably obtainable scientific, technical, economic, and other information concerning the need for, and consequences of, the intended regulation.

(8) Each agency shall identify and assess alternative forms of regulation and shall, to the extent feasible, specify performance objectives, rather than specifying the behavior or manner of compliance that regulated entities must adopt.

(9) Wherever feasible, agencies shall seek views of appropriate State, local, and tribal officials before imposing regulatory requirements that might significantly or uniquely affect those governmental entities. Each agency shall assess the effects of Federal regulations on State, local, and tribal governments, including specifically the availability of resources to carry out those mandates, and seek to minimize those burdens that uniquely or significantly affect such governmental entities, consistent with achieving regulatory objectives. In addition, as appropriate, agencies shall seek to harmonize Federal regulatory actions with related State, local, and tribal regulatory and other governmental functions.

(10) Each agency shall avoid regulations that are inconsistent, incompatible, or duplicative with its other regulations or those of other Federal agencies.

(11) Each agency shall tailor its regulations to impose the least burden on society, including individuals, businesses of differing sizes, and other entities (including small communities and governmental entities), consistent with obtaining the regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations.

(12) Each agency shall draft its regulations to be simple and easy to understand, with the goal of minimizing the potential for uncertainty and litigation arising from such uncertainty.

Sec. 2. *Organization.* An efficient regulatory planning and review process is vital to ensure that the Federal Government's regulatory system best serves the American people.

(a) *The Agencies.* Because Federal agencies are the repositories of significant substantive expertise and experience, they are responsible for developing regulations and assuring that the regulations are consistent with applicable law, the President's priorities, and the principles set forth in this Executive order.

(b) *The Office of Management and Budget.* Coordinated review of agency rulemaking is necessary to ensure that regulations are consistent with applicable law, the President's priorities, and the principles set forth in this Executive order, and that decisions made by one agency do not conflict with the policies or actions taken or planned by another agency. The Office of Management and Budget (OMB) shall carry out that review function. Within OMB, the Office of Information and Regulatory Affairs (OIRA) is the repository of expertise concerning regulatory issues, including methodologies and procedures that affect more than one agency, this Executive order, and the President's regulatory policies. To the extent permitted by law, OMB shall provide guidance to agencies and assist the President, the Vice President, and other regulatory policy advisors to the President in regulatory planning and shall be the entity that reviews individual regulations, as provided by this Executive order.

(c) *The Vice President.* The Vice President is the principal advisor to the President on, and shall coordinate the development and presentation of recommendations concerning, regulatory policy, planning, and review, as set forth in this Executive order. In fulfilling their responsibilities under this Executive order, the President and the Vice President shall be assisted by the regulatory policy advisors within the Executive Office of the President and by such agency officials and personnel as the President and the Vice President may, from time to time, consult.

Sec. 3. *Definitions.* For purposes of this Executive order: (a) ''Advisors'' refers to such regulatory policy advisors to the President as the President and Vice President may from time to time consult, including, among others: (1) the Director of OMB; (2) the Chair (or another member) of the Council of Economic Advisers; (3) the Assistant to the President for Economic Policy; (4) the Assistant to the President for Domestic Policy; (5) the Assistant to the President for National Security Affairs; (6) the Assistant to the President for Science and Technology; (7) the Assistant to the President for Intergovernmental Affairs; (8) the Assistant to the President and Staff Secretary; (9) the Assistant to the President and Chief of Staff to the Vice President; (10) the Assistant to the President and Counsel to the President; (11) the Deputy Assistant to the President and Director of the White House Office on Environmental Policy; and (12) the Administrator of OIRA, who also shall coordinate communications relating to this Executive order among the agencies, OMB, the other Advisors, and the Office of the Vice President.

(b) ''Agency,'' unless otherwise indicated, means any authority of the United States that is an ''agency'' under 44 U.S.C. 3502(1), other than those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(10).

(c) ''Director'' means the Director of OMB.

(d) ''Regulation'' or ''rule'' means an agency statement of general applicability and future effect, which the agency intends to have the force and effect of law, that is designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency. It does not, however, include:

(1) Regulations or rules issued in accordance with the formal rulemaking provisions of 5 U.S.C. 556, 557;

(2) Regulations or rules that pertain to a military or foreign affairs function of the United States, other than procurement regulations and regulations involving the import or export of non-defense articles and services;

(3) Regulations or rules that are limited to agency organization, management, or personnel matters; or

(4) Any other category of regulations exempted by the Administrator of OIRA.

(e) ''Regulatory action'' means any substantive action by an agency (normally published in the **Federal Register**) that promulgates or is expected to lead to the promulgation of a final rule or regulation, including notices

of inquiry, advance notices of proposed rulemaking, and notices of proposed rulemaking.

(f) ''Significant regulatory action'' means any regulatory action that is likely to result in a rule that may:

(1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities;

(2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another agency;

(3) Materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or

(4) Raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in this Executive order.

Sec. 4. *Planning Mechanism*. In order to have an effective regulatory program, to provide for coordination of regulations, to maximize consultation and the resolution of potential conflicts at an early stage, to involve the public and its State, local, and tribal officials in regulatory planning, and to ensure that new or revised regulations promote the President's priorities and the principles set forth in this Executive order, these procedures shall be followed, to the extent permitted by law:

(a) *Agencies' Policy Meeting.* Early in each year's planning cycle, the Vice President shall convene a meeting of the Advisors and the heads of agencies to seek a common understanding of priorities and to coordinate regulatory efforts to be accomplished in the upcoming year.

(b) *Unified Regulatory Agenda.* For purposes of this subsection, the term ''agency'' or ''agencies'' shall also include those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(10). Each agency shall prepare an agenda of all regulations under development or review, at a time and in a manner specified by the Administrator of OIRA. The description of each regulatory action shall contain, at a minimum, a regulation identifier number, a brief summary of the action, the legal authority for the action, any legal deadline for the action, and the name and telephone number of a knowledgeable agency official. Agencies may incorporate the information required under 5 U.S.C. 602 and 41 U.S.C. 402 into these agendas.

(c) *The Regulatory Plan*. For purposes of this subsection, the term ''agency'' or ''agencies'' shall also include those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(10). (1) As part of the Unified Regulatory Agenda, beginning in 1994, each agency shall prepare a Regulatory Plan (Plan) of the most important significant regulatory actions that the agency reasonably expects to issue in proposed or final form in that fiscal year or thereafter. The Plan shall be approved personally by the agency head and shall contain at a minimum:

(A) A statement of the agency's regulatory objectives and priorities and how they relate to the President's priorities;

(B) A summary of each planned significant regulatory action including, to the extent possible, alternatives to be considered and preliminary estimates of the anticipated costs and benefits;

(C) A summary of the legal basis for each such action, including whether any aspect of the action is required by statute or court order;

(D) A statement of the need for each such action and, if applicable, how the action will reduce risks to public health, safety, or the environment, as well as how the magnitude of the risk addressed by the action relates to other risks within the jurisdiction of the agency;

(E) The agency's schedule for action, including a statement of any applicable statutory or judicial deadlines; and

(F) The name, address, and telephone number of a person the public may contact for additional information about the planned regulatory action.

(2) Each agency shall forward its Plan to OIRA by June 1st of each year.

(3) Within 10 calendar days after OIRA has received an agency's Plan, OIRA shall circulate it to other affected agencies, the Advisors, and the Vice President.

(4) An agency head who believes that a planned regulatory action of another agency may conflict with its own policy or action taken or planned shall promptly notify, in writing, the Administrator of OIRA, who shall forward that communication to the issuing agency, the Advisors, and the Vice President.

(5) If the Administrator of OIRA believes that a planned regulatory action of an agency may be inconsistent with the President's priorities or the principles set forth in this Executive order or may be in conflict with any policy or action taken or planned by another agency, the Administrator of OIRA shall promptly notify, in writing, the affected agencies, the Advisors, and the Vice President.

(6) The Vice President, with the Advisors' assistance, may consult with the heads of agencies with respect to their Plans and, in appropriate instances, request further consideration or inter-agency coordination.

(7) The Plans developed by the issuing agency shall be published annually in the October publication of the Unified Regulatory Agenda. This publication shall be made available to the Congress; State, local, and tribal governments; and the public. Any views on any aspect of any agency Plan, including whether any planned regulatory action might conflict with any other planned or existing regulation, impose any unintended consequences on the public, or confer any unclaimed benefits on the public, should be directed to the issuing agency, with a copy to OIRA.

(d) *Regulatory Working Group.* Within 30 days of the date of this Executive order, the Administrator of OIRA shall convene a Regulatory Working Group (''Working Group''), which shall consist of representatives of the heads of each agency that the Administrator determines to have significant domestic regulatory responsibility, the Advisors, and the Vice President. The Administrator of OIRA shall chair the Working Group and shall periodically advise the Vice President on the activities of the Working Group. The Working Group shall serve as a forum to assist agencies in identifying and analyzing important regulatory issues (including, among others (1) the development of innovative regulatory techniques, (2) the methods, efficacy, and utility of comparative risk assessment in regulatory decision-making, and (3) the development of short forms and other streamlined regulatory approaches for small businesses and other entities). The Working Group shall meet at least quarterly and may meet as a whole or in subgroups of agencies with an interest in particular issues or subject areas. To inform its discussions, the Working Group may commission analytical studies and reports by OIRA, the Administrative Conference of the United States, or any other agency.

(e) *Conferences.* The Administrator of OIRA shall meet quarterly with representatives of State, local, and tribal governments to identify both existing and proposed regulations that may uniquely or significantly affect those governmental entities. The Administrator of OIRA shall also convene, from time to time, conferences with representatives of businesses, nongovernmental organizations, and the public to discuss regulatory issues of common concern.

Sec. 5. *Existing Regulations.* In order to reduce the regulatory burden on the American people, their families, their communities, their State, local, and tribal governments, and their industries; to determine whether regulations promulgated by the executive branch of the Federal Government have become unjustified or unnecessary as a result of changed circumstances; to confirm that regulations are both compatible with each other and not

duplicative or inappropriately burdensome in the aggregate; to ensure that all regulations are consistent with the President's priorities and the principles set forth in this Executive order, within applicable law; and to otherwise improve the effectiveness of existing regulations: (a) Within 90 days of the date of this Executive order, each agency shall submit to OIRA a program, consistent with its resources and regulatory priorities, under which the agency will periodically review its existing significant regulations to determine whether any such regulations should be modified or eliminated so as to make the agency's regulatory program more effective in achieving the regulatory objectives, less burdensome, or in greater alignment with the President's priorities and the principles set forth in this Executive order. Any significant regulations selected for review shall be included in the agency's annual Plan. The agency shall also identify any legislative mandates that require the agency to promulgate or continue to impose regulations that the agency believes are unnecessary or outdated by reason of changed circumstances.

(b) The Administrator of OIRA shall work with the Regulatory Working Group and other interested entities to pursue the objectives of this section. State, local, and tribal governments are specifically encouraged to assist in the identification of regulations that impose significant or unique burdens on those governmental entities and that appear to have outlived their justification or be otherwise inconsistent with the public interest.

(c) The Vice President, in consultation with the Advisors, may identify for review by the appropriate agency or agencies other existing regulations of an agency or groups of regulations of more than one agency that affect a particular group, industry, or sector of the economy, or may identify legislative mandates that may be appropriate for reconsideration by the Congress.

Sec. 6. *Centralized Review of Regulations.* The guidelines set forth below shall apply to all regulatory actions, for both new and existing regulations, by agencies other than those agencies specifically exempted by the Administrator of OIRA:

(a) *Agency Responsibilities.* (1) Each agency shall (consistent with its own rules, regulations, or procedures) provide the public with meaningful participation in the regulatory process. In particular, before issuing a notice of proposed rulemaking, each agency should, where appropriate, seek the involvement of those who are intended to benefit from and those expected to be burdened by any regulation (including, specifically, State, local, and tribal officials). In addition, each agency should afford the public a meaningful opportunity to comment on any proposed regulation, which in most cases should include a comment period of not less than 60 days. Each agency also is directed to explore and, where appropriate, use consensual mechanisms for developing regulations, including negotiated rulemaking.

(2) Within 60 days of the date of this Executive order, each agency head shall designate a Regulatory Policy Officer who shall report to the agency head. The Regulatory Policy Officer shall be involved at each stage of the regulatory process to foster the development of effective, innovative, and least burdensome regulations and to further the principles set forth in this Executive order.

(3) In addition to adhering to its own rules and procedures and to the requirements of the Administrative Procedure Act, the Regulatory Flexibility Act, the Paperwork Reduction Act, and other applicable law, each agency shall develop its regulatory actions in a timely fashion and adhere to the following procedures with respect to a regulatory action:

(A) Each agency shall provide OIRA, at such times and in the manner specified by the Administrator of OIRA, with a list of its planned regulatory actions, indicating those which the agency believes are significant regulatory actions within the meaning of this Executive order. Absent a material change in the development of the planned regulatory action, those not designated as significant will not be subject to review under this section unless, within 10 working days of receipt

of the list, the Administrator of OIRA notifies the agency that OIRA has determined that a planned regulation is a significant regulatory action within the meaning of this Executive order. The Administrator of OIRA may waive review of any planned regulatory action designated by the agency as significant, in which case the agency need not further comply with subsection (a)(3)(B) or subsection (a)(3)(C) of this section.

(B) For each matter identified as, or determined by the Administrator of OIRA to be, a significant regulatory action, the issuing agency shall provide to OIRA:

(i) The text of the draft regulatory action, together with a reasonably detailed description of the need for the regulatory action and an explanation of how the regulatory action will meet that need; and

(ii) An assessment of the potential costs and benefits of the regulatory action, including an explanation of the manner in which the regulatory action is consistent with a statutory mandate and, to the extent permitted by law, promotes the President's priorities and avoids undue interference with State, local, and tribal governments in the exercise of their governmental functions.

(C) For those matters identified as, or determined by the Administrator of OIRA to be, a significant regulatory action within the scope of section 3(f)(1), the agency shall also provide to OIRA the following additional information developed as part of the agency's decision-making process (unless prohibited by law):

(i) An assessment, including the underlying analysis, of benefits anticipated from the regulatory action (such as, but not limited to, the promotion of the efficient functioning of the economy and private markets, the enhancement of health and safety, the protection of the natural environment, and the elimination or reduction of discrimination or bias) together with, to the extent feasible, a quantification of those benefits;

(ii) An assessment, including the underlying analysis, of costs anticipated from the regulatory action (such as, but not limited to, the direct cost both to the government in administering the regulation and to businesses and others in complying with the regulation, and any adverse effects on the efficient functioning of the economy, private markets (including productivity, employment, and competitiveness), health, safety, and the natural environment), together with, to the extent feasible, a quantification of those costs; and

(iii) An assessment, including the underlying analysis, of costs and benefits of potentially effective and reasonably feasible alternatives to the planned regulation, identified by the agencies or the public (including improving the current regulation and reasonably viable nonregulatory actions), and an explanation why the planned regulatory action is preferable to the identified potential alternatives.

(D) In emergency situations or when an agency is obligated by law to act more quickly than normal review procedures allow, the agency shall notify OIRA as soon as possible and, to the extent practicable, comply with subsections (a)(3)(B) and (C) of this section. For those regulatory actions that are governed by a statutory or court-imposed deadline, the agency shall, to the extent practicable, schedule rulemaking proceedings so as to permit sufficient time for OIRA to conduct its review, as set forth below in subsection (b)(2) through (4) of this section.

(E) After the regulatory action has been published in the **Federal Register** or otherwise issued to the public, the agency shall:

(i) Make available to the public the information set forth in subsections (a)(3)(B) and (C);

(ii) Identify for the public, in a complete, clear, and simple manner, the substantive changes between the draft submitted to OIRA for review and the action subsequently announced; and

(iii) Identify for the public those changes in the regulatory action that were made at the suggestion or recommendation of OIRA.

(F) All information provided to the public by the agency shall be in plain, understandable language.

(b) *OIRA Responsibilities.* The Administrator of OIRA shall provide meaningful guidance and oversight so that each agency's regulatory actions are consistent with applicable law, the President's priorities, and the principles set forth in this Executive order and do not conflict with the policies or actions of another agency. OIRA shall, to the extent permitted by law, adhere to the following guidelines:

(1) OIRA may review only actions identified by the agency or by OIRA as significant regulatory actions under subsection (a)(3)(A) of this section.

(2) OIRA shall waive review or notify the agency in writing of the results of its review within the following time periods:

(A) For any notices of inquiry, advance notices of proposed rulemaking, or other preliminary regulatory actions prior to a Notice of Proposed Rulemaking, within 10 working days after the date of submission of the draft action to OIRA;

(B) For all other regulatory actions, within 90 calendar days after the date of submission of the information set forth in subsections (a)(3)(B) and (C) of this section, unless OIRA has previously reviewed this information and, since that review, there has been no material change in the facts and circumstances upon which the regulatory action is based, in which case, OIRA shall complete its review within 45 days; and

(C) The review process may be extended (1) once by no more than 30 calendar days upon the written approval of the Director and (2) at the request of the agency head.

(3) For each regulatory action that the Administrator of OIRA returns to an agency for further consideration of some or all of its provisions, the Administrator of OIRA shall provide the issuing agency a written explanation for such return, setting forth the pertinent provision of this Executive order on which OIRA is relying. If the agency head disagrees with some or all of the bases for the return, the agency head shall so inform the Administrator of OIRA in writing.

(4) Except as otherwise provided by law or required by a Court, in order to ensure greater openness, accessibility, and accountability in the regulatory review process, OIRA shall be governed by the following disclosure requirements:

(A) Only the Administrator of OIRA (or a particular designee) shall receive oral communications initiated by persons not employed by the executive branch of the Federal Government regarding the substance of a regulatory action under OIRA review;

(B) All substantive communications between OIRA personnel and persons not employed by the executive branch of the Federal Government regarding a regulatory action under review shall be governed by the following guidelines: (i) A representative from the issuing agency shall be invited to any meeting between OIRA personnel and such person(s);

(ii) OIRA shall forward to the issuing agency, within 10 working days of receipt of the communication(s), all written communications, regardless of format, between OIRA personnel and any person who is not employed by the executive branch of the Federal Government, and the dates and names of individuals involved in all substantive oral communications (including meetings to which an agency representative was invited, but did not attend, and telephone conversations between OIRA personnel and any such persons); and (iii) OIRA shall publicly disclose relevant information about such communication(s), as set forth below in subsection (b)(4)(C) of this section.

(C) OIRA shall maintain a publicly available log that shall contain, at a minimum, the following information pertinent to regulatory actions under review:

(i) The status of all regulatory actions, including if (and if so, when and by whom) Vice Presidential and Presidential consideration was requested;

(ii) A notation of all written communications forwarded to an issuing agency under subsection (b)(4)(B)(ii) of this section; and

(iii) The dates and names of individuals involved in all substantive oral communications, including meetings and telephone conversations, between OIRA personnel and any person not employed by the executive branch of the Federal Government, and the subject matter discussed during such communications.

(D) After the regulatory action has been published in the **Federal Register** or otherwise issued to the public, or after the agency has announced its decision not to publish or issue the regulatory action, OIRA shall make available to the public all documents exchanged between OIRA and the agency during the review by OIRA under this section.

(5) All information provided to the public by OIRA shall be in plain, understandable language.

Sec. 7. *Resolution of Conflicts.* To the extent permitted by law, disagreements or conflicts between or among agency heads or between OMB and any agency that cannot be resolved by the Administrator of OIRA shall be resolved by the President, or by the Vice President acting at the request of the President, with the relevant agency head (and, as appropriate, other interested government officials). Vice Presidential and Presidential consideration of such disagreements may be initiated only by the Director, by the head of the issuing agency, or by the head of an agency that has a significant interest in the regulatory action at issue. Such review will not be undertaken at the request of other persons, entities, or their agents.

Resolution of such conflicts shall be informed by recommendations developed by the Vice President, after consultation with the Advisors (and other executive branch officials or personnel whose responsibilities to the President include the subject matter at issue). The development of these recommendations shall be concluded within 60 days after review has been requested.

During the Vice Presidential and Presidential review period, communications with any person not employed by the Federal Government relating to the substance of the regulatory action under review and directed to the Advisors or their staffs or to the staff of the Vice President shall be in writing and shall be forwarded by the recipient to the affected agency(ies) for inclusion in the public docket(s). When the communication is not in writing, such Advisors or staff members shall inform the outside party that the matter is under review and that any comments should be submitted in writing.

At the end of this review process, the President, or the Vice President acting at the request of the President, shall notify the affected agency and the Administrator of OIRA of the President's decision with respect to the matter.

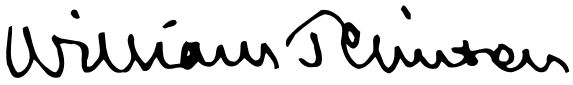
Sec. 8. *Publication.* Except to the extent required by law, an agency shall not publish in the **Federal Register** or otherwise issue to the public any regulatory action that is subject to review under section 6 of this Executive order until (1) the Administrator of OIRA notifies the agency that OIRA has waived its review of the action or has completed its review without any requests for further consideration, or (2) the applicable time period in section 6(b)(2) expires without OIRA having notified the agency that it is returning the regulatory action for further consideration under section 6(b)(3), whichever occurs first. If the terms of the preceding sentence have not been satisfied and an agency wants to publish or otherwise issue a

regulatory action, the head of that agency may request Presidential consideration through the Vice President, as provided under section 7 of this order. Upon receipt of this request, the Vice President shall notify OIRA and the Advisors. The guidelines and time period set forth in section 7 shall apply to the publication of regulatory actions for which Presidential consideration has been sought.

Sec. 9. *Agency Authority.* Nothing in this order shall be construed as displacing the agencies' authority or responsibilities, as authorized by law.

Sec. 10. *Judicial Review.* Nothing in this Executive order shall affect any otherwise available judicial review of agency action. This Executive order is intended only to improve the internal management of the Federal Government and does not create any right or benefit, substantive or procedural, enforceable at law or equity by a party against the United States, its agencies or instrumentalities, its officers or employees, or any other person.

Sec. 11. *Revocations.* Executive Orders Nos. 12291 and 12498; all amendments to those Executive orders; all guidelines issued under those orders; and any exemptions from those orders heretofore granted for any category of rule are revoked.



THE WHITE HOUSE,
September 30, 1993.

[FR citation 58 FR 51735]

Federal Register
Vol. 61, No. 26
Wednesday, February 7, 1996

Presidential Documents

Title 3—

The President

Executive Order 12988 of February 5, 1996

Civil Justice Reform

By the authority vested in me as President by the Constitution and the laws of the United States of America, including section 301 of title 3, United States Code, and in order to improve access to justice for all persons who wish to avail themselves of court and administrative adjudicatory tribunals to resolve disputes, to facilitate the just and efficient resolution of civil claims involving the United States Government, to encourage the filing of only meritorious civil claims, to improve legislative and regulatory drafting to reduce needless litigation, to promote fair and prompt adjudication before administrative tribunals, and to provide a model for similar reforms of litigation practices in the private sector and in various states, it is hereby ordered as follows:

Section 1. *Guidelines to Promote Just and Efficient Government Civil Litigation.* To promote the just and efficient resolution of civil claims, those Federal agencies and litigation counsel that conduct or otherwise participate in civil litigation on behalf of the United States Government in Federal court shall respect and adhere to the following guidelines during the conduct of such litigation:

(a) *Pre-filing Notice of a Complaint.* No litigation counsel shall file a complaint initiating civil litigation without first making a reasonable effort to notify all disputants about the nature of the dispute and to attempt to achieve a settlement, or confirming that the referring agency that previously handled the dispute has made a reasonable effort to notify the disputants and to achieve a settlement or has used its conciliation processes.

(b) *Settlement Conferences.* As soon as practicable after ascertaining the nature of a dispute in litigation, and throughout the litigation, litigation counsel shall evaluate settlement possibilities and make reasonable efforts to settle the litigation. Such efforts shall include offering to participate in a settlement conference or moving the court for a conference pursuant to Rule 16 of the Federal Rules of Civil Procedure in an attempt to resolve the dispute without additional civil litigation.

(c) *Alternative Methods of Resolving the Dispute in Litigation.* Litigation counsel shall make reasonable attempts to resolve a dispute expeditiously and properly before proceeding to trial.

(1) Whenever feasible, claims should be resolved through informal discussions, negotiations, and settlements rather than through utilization of any formal court proceeding. Where the benefits of Alternative Dispute Resolution (''ADR'') may be derived, and after consultation with the agency referring the matter, litigation counsel should suggest the use of an appropriate ADR technique to the parties.

(2) It is appropriate to use ADR techniques or processes to resolve claims of or against the United States or its agencies, after litigation counsel determines that the use of a particular technique is warranted in the context of a particular claim or claims, and that such use will materially contribute to the prompt, fair, and efficient resolution of the claims.

(3) To facilitate broader and effective use of informal and formal ADR methods, litigation counsel should be trained in ADR techniques.

(d) *Discovery.* To the extent practical, litigation counsel shall make every reasonable effort to streamline and expedite discovery in cases under counsel's supervision and control.

(1) *Review of Proposed Document Requests.* Each agency within the executive branch shall establish a coordinated procedure for the conduct and review of document discovery undertaken in litigation directly by that agency when that agency is litigation counsel. The procedure shall include, but is not necessarily limited to, review by a senior lawyer prior to service or filing of the request in litigation to determine that the request is not cumulative or duplicative, unreasonable, oppressive, unduly burdensome or expensive, taking into account the requirements of the litigation, the amount in controversy, the importance of the issues at stake in the litigation, and whether the documents can be obtained from some other source that is more convenient, less burdensome, or less expensive.

(2) *Discovery Motions.* Before petitioning a court to resolve a discovery motion or petitioning a court to impose sanctions for discovery abuses, litigation counsel shall attempt to resolve the dispute with opposing counsel. If litigation counsel makes a discovery motion concerning the dispute, he or she shall represent in that motion that any attempt at resolution was unsuccessful or impracticable under the circumstances.

(e) *Sanctions.* Litigation counsel shall take steps to seek sanctions against opposing counsel and opposing parties where appropriate.

(1) Litigation counsel shall evaluate filings made by opposing parties and, where appropriate, shall petition the court to impose sanctions against those responsible for abusive practices.

(2) Prior to filing a motion for sanctions, litigation counsel shall submit the motion for review to the sanctions officer, or his or her designee, within the litigation counsel's agency. Such officer or designee shall be a senior supervising attorney within the agency, and shall be licensed to practice law before a State court, courts of the District of Columbia, or courts of any territory or Commonwealth of the United States. The sanctions officer or designee shall also review motions for sanctions that are filed against litigation counsel, the United States, its agencies, or its officers.

(f) *Improved Use of Litigation Resources.* Litigation counsel shall employ efficient case management techniques and shall make reasonable efforts to expedite civil litigation in cases under that counsel's supervision and control. This includes but is not limited to:

(1) making reasonable efforts to negotiate with other parties about, and stipulate to, facts that are not in dispute;

(2) reviewing and revising pleadings and other filings to ensure that they are accurate and that they reflect a narrowing of issues, if any, that has resulted from discovery;

(3) requesting early trial dates where practicable;

(4) moving for summary judgment in every case where the movant would be likely to prevail, or where the motion is likely to narrow the issues to be tried; and

(5) reviewing and revising pleadings and other filings to ensure that unmeritorious threshold defenses and jurisdictional arguments, resulting in unnecessary delay, are not raised.

Sec. 2. *Government Pro Bono and Volunteer Service.* All Federal agencies should develop appropriate programs to encourage and facilitate pro bono legal and other volunteer service by government employees to be performed on their own time, including attorneys, as permitted by statute, regulation, or other rule or guideline.

Sec. 3. *Principles to Enact Legislation and Promulgate Regulations Which Do Not Unduly Burden the Federal Court System.*

(a) *General Duty to Review Legislation and Regulations.* Within current budgetary constraints and existing executive branch coordination mechanisms and procedures established in OMB Circular A-19 and Executive Order No. 12866, each agency promulgating new regulations, reviewing existing regulations, developing legislative proposals concerning regulations, and developing new legislation shall adhere to the following requirements:

(1) The agency's proposed legislation and regulations shall be reviewed by the agency to eliminate drafting errors and ambiguity;

(2) The agency's proposed legislation and regulations shall be written to minimize litigation; and

(3) The agency's proposed legislation and regulations shall provide a clear legal standard for affected conduct rather than a general standard, and shall promote simplification and burden reduction.

(b) *Specific Issues for Review.* In conducting the reviews required by subsection (a), each agency formulating proposed legislation and regulations shall make every reasonable effort to ensure:

(1) that the legislation, as appropriate—

(A) specifies whether all causes of action arising under the law are subject to statutes of limitations;

(B) specifies in clear language the preemptive effect, if any, to be given to the law;

(C) specifies in clear language the effect on existing Federal law, if any, including all provisions repealed, circumscribed, displaced, impaired, or modified;

(D) provides a clear legal standard for affected conduct;

(E) specifies whether private arbitration and other forms of private dispute resolution are appropriate under enforcement and relief provisions; subject to constitutional requirements;

(F) specifies whether the provisions of the law are severable if one or more of them is found to be unconstitutional;

(G) specifies in clear language the retroactive effect, if any, to be given to the law;

(H) specifies in clear language the applicable burdens of proof;

(I) specifies in clear language whether it grants private parties a right to sue and, if so, the relief available and the conditions and terms for authorized awards of attorney's fees, if any;

(J) specifies whether State courts have jurisdiction under the law and, if so, whether and under what conditions an action would be removable to Federal court;

(K) specifies whether administrative proceedings are to be required before parties may file suit in court and, if so, describes those proceedings and requires the exhaustion of administrative remedies;

(L) sets forth the standards governing the assertion of personal jurisdiction, if any;

(M) defines key statutory terms, either explicitly or by reference to other statutes that explicitly define those terms;

(N) specifies whether the legislation applies to the Federal Government or its agencies;

(O) specifies whether the legislation applies to States, territories, the District of Columbia, and the Commonwealths of Puerto Rico and of the Northern Mariana Islands;

(P) specifies what remedies are available such as money damages, civil penalties, injunctive relief, and attorney's fees; and

(Q) addresses other important issues affecting clarity and general draftsmanship of legislation set forth by the Attorney General, with the concurrence of the Director of the Office of Management and Budget (''OMB'') and after consultation with affected agencies, that are determined to be in accordance with the purposes of this order.

(2) that the regulation, as appropriate—

(A) specifies in clear language the preemptive effect, if any, to be given to the regulation;

(B) specifies in clear language the effect on existing Federal law or regulation, if any, including all provisions repealed, circumscribed, displaced, impaired, or modified;

(C) provides a clear legal standard for affected conduct rather than a general standard, while promoting simplification and burden reduction;

(D) specifies in clear language the retroactive effect, if any, to be given to the regulation;

(E) specifies whether administrative proceedings are to be required before parties may file suit in court and, if so, describes those proceedings and requires the exhaustion of administrative remedies;

(F) defines key terms, either explicitly or by reference to other regulations or statutes that explicitly define those items; and

(G) addresses other important issues affecting clarity and general draftsmanship of regulations set forth by the Attorney General, with the concurrence of the Director of OMB and after consultation with affected agencies, that are determined to be in accordance with the purposes of this order.

(c) *Agency Review.* The agencies shall review such draft legislation or regulation to determine that either the draft legislation or regulation meets the applicable standards provided in subsections (a) and (b) of this section, or it is unreasonable to require the particular piece of draft legislation or regulation to meet one or more of those standards.

Sec. 4. *Principles to Promote Just and Efficient Administrative Adjudications.*

(a) *Implementation of Administrative Conference Recommendations.* In order to promote just and efficient resolution of disputes, an agency that adjudicates administrative claims shall, to the extent reasonable and practicable, and when not in conflict with other sections of this order, implement the recommendations of the Administrative Conference of the United States, entitled ''Case Management as a Tool for Improving Agency Adjudication,'' as contained in 1 C.F.R. 305.86-7 (1991).

(b) *Improvements in Administrative Adjudication.* All Federal agencies should review their administrative adjudicatory processes and develop specific procedures to reduce delay in decision-making, to facilitate self-representation where appropriate, to expand non-lawyer counseling and representation where appropriate, and to invest maximum discretion in fact-finding officers to encourage appropriate settlement of claims as early as possible.

(c) *Bias.* All Federal agencies should review their administrative adjudicatory processes to identify any type of bias on the part of the decision-makers that results in an injustice to persons who appear before administrative adjudicatory tribunals; regularly train all fact-finders, administrative law judges, and other decision-makers to eliminate such bias; and establish appropriate mechanisms to receive and resolve complaints of such bias from persons who appear before administrative adjudicatory tribunals.

(d) *Public Education.* All Federal agencies should develop effective and simple methods, including the use of electronic technology, to educate the public about its claims/benefits policies and procedures.

Sec. 5. *Coordination by the Department of Justice.*

(a) The Attorney General shall coordinate efforts by Federal agencies to implement sections 1, 2 and 4 of this order.

(b) To implement the principles and purposes announced by this order, the Attorney General is authorized to issue guidelines implementing sections 1 and 4 of this order for the Department of Justice. Such guidelines shall serve as models for internal guidelines that may be issued by other agencies pursuant to this order.

Sec. 6. *Definitions.* For purposes of this order:

(a) The term ''agency'' shall be defined as that term is defined in section 105 of title 5, United States Code.

(b) The term ''litigation counsel'' shall be defined as the trial counsel or the office in which such trial counsel is employed, such as the United States Attorney's Office for the district in which the litigation is pending or a litigating division of the Department of Justice. Special Assistant United States Attorneys are included within this definition. Those agencies authorized by law to represent themselves in court without assistance from the Department of Justice are also included in this definition, as are private counsel hired by any Federal agency to conduct litigation on behalf of the agency or the United States.

Sec. 7. *No Private Rights Created.* This order is intended only to improve the internal management of the executive branch in resolving disputes, conducting litigation in a reasonable and just manner, and reviewing legislation and regulations. This order shall not be construed as creating any right or benefit, substantive or procedural, enforceable at law or in equity by a party against the United States, its agencies, its officers, or any other person. This order shall not be construed to create any right to judicial review involving the compliance or noncompliance of the United States, its agencies, its officers, or any other person with this order. Nothing in this order shall be construed to obligate the United States to accept a particular settlement or resolution of a dispute, to alter its standards for accepting settlements, to forego seeking a consent decree or other relief, or to alter any existing delegation of settlement or litigating authority.

Sec. 8. *Scope.*

(a) *No Applicability to Criminal Matters or Proceedings in Foreign Courts.* This order is applicable to civil matters only. It is not intended to affect criminal matters, including enforcement of criminal fines or judgments of criminal forfeiture. This order does not apply to litigation brought by or against the United States in foreign courts or tribunals.

(b) *Application of Notice Provision.* Notice pursuant to subsection (a) of section 1 is not required (1) in any action to seize or forfeit assets subject to forfeiture or in any action to seize property; (2) in any bankruptcy, insolvency, conservatorship, receivership, or liquidation proceeding; (3) when the assets that are the subject of the action or that would satisfy the judgment are subject to flight, dissipation, or destruction; (4) when the defendant is subject to flight; (5) when, as determined by litigation counsel, exigent circumstances make providing such notice impracticable or such notice would otherwise defeat the purpose of the litigation, such as in actions seeking temporary restraining orders or preliminary injunctive relief; or (6) in those limited classes of cases where the Attorney General determines that providing such notice would defeat the purpose of the litigation.

(c) *Additional Guidance as to Scope.* The Attorney General shall have the authority to issue further guidance as to the scope of this order, except section 3, consistent with the purposes of this order.

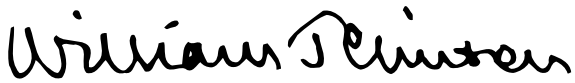
Sec. 9. *Conflicts with Other Rules.* Nothing in this order shall be construed to require litigation counsel or any agency to act in a manner contrary to the Federal Rules of Civil Procedure, Tax Court Rules of Practice and Procedure, State or Federal law, other applicable rules of practice or procedure, or court order.

Sec. 10. *Privileged Information.* Nothing in this order shall compel or authorize the disclosure of privileged information, sensitive law enforcement infor-

mation, information affecting national security, or information the disclosure of which is prohibited by law.

Sec. 11. *Effective Date.* This order shall become effective 90 days after the date of signature. This order shall not apply to litigation commenced prior to the effective date.

Sec. 12. *Revocation.* Executive Order No. 12778 is hereby revoked.



THE WHITE HOUSE,
February 5, 1996.

[FR Doc. 96–2755
Filed 2–6–96; 8:45 am]
Billing code 3195–01–P

Federal Register
Vol. 63, No. 96
Tuesday, May 19, 1998

Presidential Documents

Title 3—

The President

Executive Order 13083 of May 14, 1998

Federalism

By the authority vested in me as President by the Constitution and the laws of the United States of America, and in order to guarantee the division of governmental responsibilities, embodied in the Constitution, between the Federal Government and the States that was intended by the Framers and application of those principles by the Executive departments and agencies in the formulation and implementation of policies, it is hereby ordered as follows:

Section 1. *Definitions.* For purposes of this order:

(a) ''State'' or ''States'' refer to the States of the United States of America, individually or collectively, and, where relevant, to State governments, including units of local government and other political subdivisions established by the States.

(b) ''Policies that have federalism implications'' refers to Federal regulations, proposed legislation, and other policy statements or actions that have substantial direct effects on the States or on the relationship, or the distribution of power and responsibilities, between the Federal Government and the States.

(c) ''Agency'' means any authority of the United States that is an ''agency'' under 44 U.S.C. 3502(1), other than those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(5).

Sec. 2. *Fundamental Federalism Principles.* In formulating and implementing policies that have federalism implications, agencies shall be guided by the following fundamental federalism principles:

(a) The structure of government established by the Constitution is premised upon a system of checks and balances.

(b) The Constitution created a Federal Government of supreme, but limited, powers. The sovereign powers not granted to the Federal Government are reserved to the people or to the States, unless prohibited to the States by the Constitution.

(c) Federalism reflects the principle that dividing power between the Federal Government and the States serves to protect individual liberty. Preserving State authority provides an essential balance to the power of the Federal Government, while preserving the supremacy of Federal law provides an essential balance to the power of the States.

(d) The people of the States are at liberty, subject only to the limitations in the Constitution itself or in Federal law, to define the moral, political, and legal character of their lives.

(e) Our constitutional system encourages a healthy diversity in the public policies adopted by the people of the several States according to their own conditions, needs, and desires. States and local governments are often uniquely situated to discern the sentiments of the people and to govern accordingly.

(f) Effective public policy is often achieved when there is competition among the several States in the fashioning of different approaches to public policy issues. The search for enlightened public policy is often furthered when individual States and local governments are free to experiment with a variety of approaches to public issues. Uniform, national approaches to

public policy problems can inhibit the creation of effective solutions to those problems.

(g) Policies of the Federal Government should recognize the responsibility of—and should encourage opportunities for—States, local governments, private associations, neighborhoods, families, and individuals to achieve personal, social, environmental, and economic objectives through cooperative effort.

Sec. 3. *Federalism Policymaking Criteria.* In addition to adhering to the fundamental federalism principles set forth in section 2 of this order, agencies shall adhere, to the extent permitted by law, to the following criteria when formulating and implementing policies that have federalism implications:

(a) There should be strict adherence to constitutional principles. Agencies should closely examine the constitutional and statutory authority supporting any Federal action that would limit the policymaking discretion of States and local governments, and should carefully assess the necessity for such action.

(b) Agencies may limit the policymaking discretion of States and local governments only after determining that there is constitutional and legal authority for the action.

(c) With respect to Federal statutes and regulations administered by States and local governments, the Federal Government should grant States and local governments the maximum administrative discretion possible. Any Federal oversight of such State and local administration should not unnecessarily intrude on State and local discretion.

(d) It is important to recognize the distinction between matters of national or multi-state scope (which may justify Federal action) and matters that are merely common to the States (which may not justify Federal action because individual States, acting individually or together, may effectively deal with them). Matters of national or multi-state scope that justify Federal action may arise in a variety of circumstances, including:

(1) When the matter to be addressed by Federal action occurs interstate as opposed to being contained within one State's boundaries.

(2) When the source of the matter to be addressed occurs in a State different from the State (or States) where a significant amount of the harm occurs.

(3) When there is a need for uniform national standards.

(4) When decentralization increases the costs of government thus imposing additional burdens on the taxpayer.

(5) When States have not adequately protected individual rights and liberties.

(6) When States would be reluctant to impose necessary regulations because of fears that regulated business activity will relocate to other States.

(7) When placing regulatory authority at the State or local level would undermine regulatory goals because high costs or demands for specialized expertise will effectively place the regulatory matter beyond the resources of State authorities.

(8) When the matter relates to Federally owned or managed property or natural resources, trust obligations, or international obligations.

(9) When the matter to be regulated significantly or uniquely affects Indian tribal governments.

Sec. 4. *Consultation.* (a) Each agency shall have an effective process to permit elected officials and other representatives of State and local governments to provide meaningful and timely input in the development of regulatory policies that have federalism implications.

(b) To the extent practicable and permitted by law, no agency shall promulgate any regulation that is not required by statute, that has federalism implica-

tions, and that imposes substantial direct compliance costs on States and local governments, unless:

(1) funds necessary to pay the direct costs incurred by the State or local government in complying with the regulation are provided by the Federal Government; or

(2) the agency, prior to the formal promulgation of the regulation,

(A) in a separately identified portion of the preamble to the regulation as it is to be issued in the **Federal Register**, provides to the Director of the Office of Management and Budget a description of the extent of the agency's prior consultation with representatives of affected States and local governments, a summary of the nature of their concerns, and the agency's position supporting the need to issue the regulation; and

(B) makes available to the Director of the Office of Management and Budget any written communications submitted to the agency by States or local governments.

Sec. 5. *Increasing Flexibility for State and Local Waivers.* (a) Agencies shall review the processes under which States and local governments apply for waivers of statutory and regulatory requirements and take appropriate steps to streamline those processes.

(b) Each agency shall, to the extent practicable and permitted by law, consider any application by a State or local government for a waiver of statutory or regulatory requirements in connection with any program administered by that agency with a general view toward increasing opportunities for utilizing flexible policy approaches at the State or local level in cases in which the proposed waiver is consistent with applicable Federal policy objectives and is otherwise appropriate.

(c) Each agency shall, to the extent practicable and permitted by law, render a decision upon a complete application for a waiver within 120 days of receipt of such application by the agency. If the application for a waiver is not granted, the agency shall provide the applicant with timely written notice of the decision and the reasons therefor.

(d) This section applies only to statutory or regulatory requirements that are discretionary and subject to waiver by the agency.

Sec. 6. *Independent Agencies.* Independent regulatory agencies are encouraged to comply with the provisions of this order.

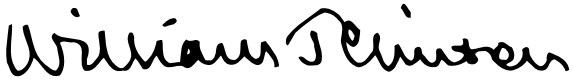
Sec. 7. *General Provisions.* (a) This order is intended only to improve the internal management of the executive branch and is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or equity by a party against the United States, its agencies or instrumentalities, its officers or employees, or any other person.

(b) This order shall supplement but not supersede the requirements contained in Executive Order 12866 (''Regulatory Planning and Review''), Executive Order 12988 (''Civil Justice Reform''), and OMB Circular A–19.

(c) Executive Order 12612 of October 26, 1987, and Executive Order 12875 of October 26, 1993, are revoked.

(d) The consultation and waiver provisions in sections 4 and 5 of this order shall complement the Executive order entitled, ''Consultation and Coordination with Indian Tribal Governments,'' being issued on this day.

(e) This order shall be effective 90 days after the date of this order.



THE WHITE HOUSE,
May 14, 1998.

[FR Doc. 98–13552
Filed 5–19–98; 11:24 am]
Billing code 3195–01–P

Federal Register
Vol. 64, No. 153
Tuesday, August 10, 1999

Presidential Documents

Title 3—

The President

Executive Order 13132 of August 4, 1999

Federalism

By the authority vested in me as President by the Constitution and the laws of the United States of America, and in order to guarantee the division of governmental responsibilities between the national government and the States that was intended by the Framers of the Constitution, to ensure that the principles of federalism established by the Framers guide the executive departments and agencies in the formulation and implementation of policies, and to further the policies of the Unfunded Mandates Reform Act, it is hereby ordered as follows:

Section 1. *Definitions.* For purposes of this order:

(a) ''Policies that have federalism implications'' refers to regulations, legislative comments or proposed legislation, and other policy statements or actions that have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

(b) ''State'' or ''States'' refer to the States of the United States of America, individually or collectively, and, where relevant, to State governments, including units of local government and other political subdivisions established by the States.

(c) ''Agency'' means any authority of the United States that is an ''agency'' under 44 U.S.C. 3502(1), other than those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(5).

(d) ''State and local officials'' means elected officials of State and local governments or their representative national organizations.

Sec. 2. *Fundamental Federalism Principles.* In formulating and implementing policies that have federalism implications, agencies shall be guided by the following fundamental federalism principles:

(a) Federalism is rooted in the belief that issues that are not national in scope or significance are most appropriately addressed by the level of government closest to the people.

(b) The people of the States created the national government and delegated to it enumerated governmental powers. All other sovereign powers, save those expressly prohibited the States by the Constitution, are reserved to the States or to the people.

(c) The constitutional relationship among sovereign governments, State and national, is inherent in the very structure of the Constitution and is formalized in and protected by the Tenth Amendment to the Constitution.

(d) The people of the States are free, subject only to restrictions in the Constitution itself or in constitutionally authorized Acts of Congress, to define the moral, political, and legal character of their lives.

(e) The Framers recognized that the States possess unique authorities, qualities, and abilities to meet the needs of the people and should function as laboratories of democracy.

(f) The nature of our constitutional system encourages a healthy diversity in the public policies adopted by the people of the several States according to their own conditions, needs, and desires. In the search for enlightened public policy, individual States and communities are free to experiment with a variety of approaches to public issues. One-size-fits-all approaches to public policy problems can inhibit the creation of effective solutions to those problems.

(g) Acts of the national government—whether legislative, executive, or judicial in nature—that exceed the enumerated powers of that government under the Constitution violate the principle of federalism established by the Framers.

(h) Policies of the national government should recognize the responsibility of—and should encourage opportunities for—individuals, families, neighborhoods, local governments, and private associations to achieve their personal, social, and economic objectives through cooperative effort.

(i) The national government should be deferential to the States when taking action that affects the policymaking discretion of the States and should act only with the greatest caution where State or local governments have identified uncertainties regarding the constitutional or statutory authority of the national government.

Sec. 3. *Federalism Policymaking Criteria.* In addition to adhering to the fundamental federalism principles set forth in section 2, agencies shall adhere, to the extent permitted by law, to the following criteria when formulating and implementing policies that have federalism implications:

(a) There shall be strict adherence to constitutional principles. Agencies shall closely examine the constitutional and statutory authority supporting any action that would limit the policymaking discretion of the States and shall carefully assess the necessity for such action. To the extent practicable, State and local officials shall be consulted before any such action is implemented. Executive Order 12372 of July 14, 1982 (''Intergovernmental Review of Federal Programs'') remains in effect for the programs and activities to which it is applicable.

(b) National action limiting the policymaking discretion of the States shall be taken only where there is constitutional and statutory authority for the action and the national activity is appropriate in light of the presence of a problem of national significance. Where there are significant uncertainties as to whether national action is authorized or appropriate, agencies shall consult with appropriate State and local officials to determine whether Federal objectives can be attained by other means.

(c) With respect to Federal statutes and regulations administered by the States, the national government shall grant the States the maximum administrative discretion possible. Intrusive Federal oversight of State administration is neither necessary nor desirable.

(d) When undertaking to formulate and implement policies that have federalism implications, agencies shall:

(1) encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States;

(2) where possible, defer to the States to establish standards;

(3) in determining whether to establish uniform national standards, consult with appropriate State and local officials as to the need for national standards and any alternatives that would limit the scope of national standards or otherwise preserve State prerogatives and authority; and

(4) where national standards are required by Federal statutes, consult with appropriate State and local officials in developing those standards.

Sec. 4. *Special Requirements for Preemption.* Agencies, in taking action that preempts State law, shall act in strict accordance with governing law.

(a) Agencies shall construe, in regulations and otherwise, a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.

(b) Where a Federal statute does not preempt State law (as addressed in subsection (a) of this section), agencies shall construe any authorization in the statute for the issuance of regulations as authorizing preemption of State law by rulemaking only when the exercise of State authority directly conflicts with the exercise of Federal authority under the Federal statute or there is clear evidence to conclude that the Congress intended the agency to have the authority to preempt State law.

(c) Any regulatory preemption of State law shall be restricted to the minimum level necessary to achieve the objectives of the statute pursuant to which the regulations are promulgated.

(d) When an agency foresees the possibility of a conflict between State law and Federally protected interests within its area of regulatory responsibility, the agency shall consult, to the extent practicable, with appropriate State and local officials in an effort to avoid such a conflict.

(e) When an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.

Sec. 5. *Special Requirements for Legislative Proposals.* Agencies shall not submit to the Congress legislation that would:

(a) directly regulate the States in ways that would either interfere with functions essential to the States' separate and independent existence or be inconsistent with the fundamental federalism principles in section 2;

(b) attach to Federal grants conditions that are not reasonably related to the purpose of the grant; or

(c) preempt State law, unless preemption is consistent with the fundamental federalism principles set forth in section 2, and unless a clearly legitimate national purpose, consistent with the federalism policymaking criteria set forth in section 3, cannot otherwise be met.

Sec. 6. *Consultation.*

(a) Each agency shall have an accountable process to ensure meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications. Within 90 days after the effective date of this order, the head of each agency shall designate an official with principal responsibility for the agency's implementation of this order and that designated official shall submit to the Office of Management and Budget a description of the agency's consultation process.

(b) To the extent practicable and permitted by law, no agency shall promulgate any regulation that has federalism implications, that imposes substantial direct compliance costs on State and local governments, and that is not required by statute, unless:

(1) funds necessary to pay the direct costs incurred by the State and local governments in complying with the regulation are provided by the Federal Government; or

(2) the agency, prior to the formal promulgation of the regulation,

(A) consulted with State and local officials early in the process of developing the proposed regulation;

(B) in a separately identified portion of the preamble to the regulation as it is to be issued in the **Federal Register**, provides to the Director of the Office of Management and Budget a federalism summary impact statement, which consists of a description of the extent of the agency's prior consultation with State and local officials, a summary of the nature of their concerns and the agency's position supporting the need to issue the regulation, and a statement of the extent to which the concerns of State and local officials have been met; and

(C) makes available to the Director of the Office of Management and Budget any written communications submitted to the agency by State and local officials.

(c) To the extent practicable and permitted by law, no agency shall promulgate any regulation that has federalism implications and that preempts State law, unless the agency, prior to the formal promulgation of the regulation,

(1) consulted with State and local officials early in the process of developing the proposed regulation;

(2) in a separately identified portion of the preamble to the regulation as it is to be issued in the **Federal Register**, provides to the Director of the Office of Management and Budget a federalism summary impact statement, which consists of a description of the extent of the agency's prior consultation with State and local officials, a summary of the nature of their concerns and the agency's position supporting the need to issue the regulation, and a statement of the extent to which the concerns of State and local officials have been met; and

(3) makes available to the Director of the Office of Management and Budget any written communications submitted to the agency by State and local officials.

Sec. 7. *Increasing Flexibility for State and Local Waivers.*

(a) Agencies shall review the processes under which State and local governments apply for waivers of statutory and regulatory requirements and take appropriate steps to streamline those processes.

(b) Each agency shall, to the extent practicable and permitted by law, consider any application by a State for a waiver of statutory or regulatory requirements in connection with any program administered by that agency with a general view toward increasing opportunities for utilizing flexible policy approaches at the State or local level in cases in which the proposed waiver is consistent with applicable Federal policy objectives and is otherwise appropriate.

(c) Each agency shall, to the extent practicable and permitted by law, render a decision upon a complete application for a waiver within 120 days of receipt of such application by the agency. If the application for a waiver is not granted, the agency shall provide the applicant with timely written notice of the decision and the reasons therefor.

(d) This section applies only to statutory or regulatory requirements that are discretionary and subject to waiver by the agency.

Sec. 8. *Accountability.*

(a) In transmitting any draft final regulation that has federalism implications to the Office of Management and Budget pursuant to Executive Order 12866 of September 30, 1993, each agency shall include a certification from the official designated to ensure compliance with this order stating that the requirements of this order have been met in a meaningful and timely manner.

(b) In transmitting proposed legislation that has federalism implications to the Office of Management and Budget, each agency shall include a certification from the official designated to ensure compliance with this order that all relevant requirements of this order have been met.

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(c) Within 180 days after the effective date of this order, the Director of the Office of Management and Budget and the Assistant to the President for Intergovernmental Affairs shall confer with State and local officials to ensure that this order is being properly and effectively implemented.

Sec. 9. *Independent Agencies.* Independent regulatory agencies are encouraged to comply with the provisions of this order.

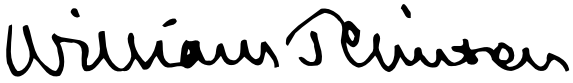
Sec. 10. *General Provisions.*

(a) This order shall supplement but not supersede the requirements contained in Executive Order 12372 (''Intergovernmental Review of Federal Programs''), Executive Order 12866 (''Regulatory Planning and Review''), Executive Order 12988 (''Civil Justice Reform''), and OMB Circular A–19.

(b) Executive Order 12612 (''Federalism''), Executive Order 12875 (''Enhancing the Intergovernmental Partnership''), Executive Order 13083 (''Federalism''), and Executive Order 13095 (''Suspension of Executive Order 13083'') are revoked.

(c) This order shall be effective 90 days after the date of this order.

Sec. 11. *Judicial Review.* This order is intended only to improve the internal management of the executive branch, and is not intended to create any right or benefit, substantive or procedural, enforceable at law by a party against the United States, its agencies, its officers, or any person.



THE WHITE HOUSE,
August 4, 1999.

[FR Doc. 99–20729
Filed 8–9–99; 8:45 am]
Billing code 3195–01–P

FUERST ITTLEMAN DAVID & JOSEPH PL

ADDENDUM 8

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tum by weight of moisture. The fat content is not over 1½ per centum by weight unless otherwise indicated.

The term ''milk'', when used herein, means sweet milk of cows.

(Mar. 2, 1944, ch. 77, 58 Stat. 108; July 2, 1956, ch. 495, 70 Stat. 486.)

REFERENCES IN TEXT

The Federal Food, Drug, and Cosmetic Act of June 26, 1938 (ch. 675, sec. 1, 52 Stat. 1040), referred to in text, probably means act June 25, 1938, ch. 675, 52 Stat. 1040, as amended, which is classified generally to this chapter (§ 301 et seq.). For complete classification of this Act to the Code, see section 301 of this title and Tables.

CODIFICATION

Section was not enacted as a part of the Federal Food, Drug, and Cosmetic Act which comprises this chapter, but was made applicable thereto.

AMENDMENTS

1956—Act July 2, 1956, substituted ''nonfat dry milk'' for ''nonfat dry milk solids or defatted milk solids''.

§ 321d. Market names for catfish and ginseng

(a) Catfish labeling

(1) In general

Notwithstanding any other provision of law, for purposes of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.)—

(A) the term ''catfish'' may only be considered to be a common or usual name (or part thereof) for fish classified within the family Ictaluridae; and

(B) only labeling or advertising for fish classified within that family may include the term ''catfish''.

(2) Omitted

(b) Ginseng labeling

(1) In general

Notwithstanding any other provision of law, for purposes of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.)—

(A) the term ''ginseng'' may only be considered to be a common or usual name (or part thereof) for any herb or herbal ingredient derived from a plant classified within the genus Panax; and

(B) only labeling or advertising for herbs or herbal ingredients classified within that genus may include the term ''ginseng''.

(2) Omitted

(Pub. L. 107–171, title X, § 10806, May 13, 2002, 116 Stat. 526.)

REFERENCES IN TEXT

The Federal Food, Drug, and Cosmetic Act, referred to in subsecs. (a)(1), (b)(1), is act June 25, 1938, ch. 675, 52 Stat. 1040, as amended, which is classified generally to this chapter. For complete classification of this Act to the Code, see section 301 of this title and Tables.

CODIFICATION

Section is comprised of section 10806 of Pub. L. 107–171. Subsecs. (a)(2) and (b)(2) of section 10806 of Pub. L. 107–171 amended section 343 of this title.

Section was enacted as part of the Farm Security and Rural Investment Act of 2002, and not as part of Federal Food, Drug, and Cosmetic Act which comprises this chapter.

SUBCHAPTER III—PROHIBITED ACTS AND PENALTIES

§ 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb–3 of this title.

(e) The refusal to permit access to or copying of any record as required by section 350a, 350c, 350f(j), 350e, 354, 360bbb–3, 373, 374(a), 379aa, or 379aa–1 of this title; or the failure to establish or maintain any record, or make any report, required under section 350a, 350c(b), 350f, 350e, 354, 355(i) or (k), 360b(a)(4)(C), 360b(j), (*l*) or (m), 360ccc–1(i), 360e(f), 360i, 360bbb–3, 379aa, 379aa–1, 387i, or 387t of this title or the refusal to permit access to or verification or copying of any such required record; or the violation of any record-keeping requirement under section 2223[1] of this title (except when such violation is committed by a farm).

(f) The refusal to permit entry or inspection as authorized by section 374 of this title.

(g) The manufacture within any Territory of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(h) The giving of a guaranty or undertaking referred to in section 333(c)(2) of this title, which guaranty or undertaking is false, except by a person who relied upon a guaranty or undertaking to the same effect signed by, and containing the name and address of, the person residing in the United States from whom he received in good faith the food, drug, device, tobacco product, or cosmetic; or the giving of a guaranty or undertaking referred to in section 333(c)(3) of this title, which guaranty or undertaking is false.

(i)(1) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp, tag, label, or other identification device authorized or required by regulations promulgated under the provisions of section 344 or 379e of this title.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing any punch, die, plate, stone, or other thing designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any drug or container or labeling thereof so as to render such drug a counterfeit drug.

(3) The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing,

[1] See References in Text note below.

or the holding for sale or dispensing, of a counterfeit drug.

(j) The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this chapter, any information acquired under authority of section 344, 348, 350a, 350c, 355, 360, 360b, 360c, 360d, 360e, 360f, 360h, 360i, 360j, 360ccc, 360ccc–1, 360ccc–2, 374, 379, 379e, 387d, 387e, 387f, 387g, 387h, 387i, or 387t(b) of this title concerning any method or process which as a trade secret is entitled to protection; or the violating of section 346a(i)(2) of this title or any regulation issued under that section..[2] This paragraph does not authorize the withholding of information from either House of Congress or from, to the extent of matter within its jurisdiction, any committee or subcommittee of such committee or any joint committee of Congress or any subcommittee of such joint committee.

(k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

(*l*) Repealed. Pub. L. 105–115, title IV, § 421, Nov. 21, 1997, 111 Stat. 2380.

(m) The sale or offering for sale of colored oleomargarine or colored margarine, or the possession or serving of colored oleomargarine or colored margarine in violation of subsections (b) or (c) of section 347 of this title.

(n) The using, in labeling, advertising or other sales promotion of any reference to any report or analysis furnished in compliance with section 374 of this title.

(*o*) In the case of a prescription drug distributed or offered for sale in interstate commerce, the failure of the manufacturer, packer, or distributor thereof to maintain for transmittal, or to transmit, to any practitioner licensed by applicable State law to administer such drug who makes written request for information as to such drug, true and correct copies of all printed matter which is required to be included in any package in which that drug is distributed or sold, or such other printed matter as is approved by the Secretary. Nothing in this paragraph shall be construed to exempt any person from any labeling requirement imposed by or under other provisions of this chapter.

(p) The failure to register in accordance with section 360 or 387e of this title, the failure to provide any information required by section 360(j), 360(k), 387e(i), or 387e(j) of this title, or the failure to provide a notice required by section 360(j)(2) or 387e(i)(3) of this title.

(q)(1) The failure or refusal—

(A) to comply with any requirement prescribed under section 360h, 360j(g), 387c(b), 387g, 387h, or 387*o* of this title;

(B) to furnish any notification or other material or information required by or under section 360i, 360j(g), 387d, 387i, or 387t of this title; or

(C) to comply with a requirement under section 360*l* or 387m of this title.

(2) With respect to any device or tobacco product, the submission of any report that is required by or under this chapter that is false or misleading in any material respect.

(r) The movement of a device or tobacco product in violation of an order under section 334(g) of this title or the removal or alteration of any mark or label required by the order to identify the device or tobacco product as detained.

(s) The failure to provide the notice required by section 350a(c) or 350a(e) of this title, the failure to make the reports required by section 350a(f)(1)(B) of this title, the failure to retain the records required by section 350a(b)(4) of this title, or the failure to meet the requirements prescribed under section 350a(f)(3) of this title.

(t) The importation of a drug in violation of section 381(d)(1) of this title, the sale, purchase, or trade of a drug or drug sample or the offer to sell, purchase, or trade a drug or drug sample in violation of section 353(c) of this title, the sale, purchase, or trade of a coupon, the offer to sell, purchase, or trade such a coupon, or the counterfeiting of such a coupon in violation of section 353(c)(2) of this title, the distribution of a drug sample in violation of section 353(d) of this title or the failure to otherwise comply with the requirements of section 353(d) of this title, or the distribution of drugs in violation of section 353(e) of this title or the failure to otherwise comply with the requirements of section 353(e) of this title.

(u) The failure to comply with any requirements of the provisions of, or any regulations or orders of the Secretary, under section 360b(a)(4)(A), 360b(a)(4)(D), or 360b(a)(5) of this title.

(v) The introduction or delivery for introduction into interstate commerce of a dietary supplement that is unsafe under section 350b of this title.

(w) The making of a knowingly false statement in any statement, certificate of analysis, record, or report required or requested under section 381(d)(3) of this title; the failure to submit a certificate of analysis as required under such section; the failure to maintain records or to submit records or reports as required by such section; the release into interstate commerce of any article or portion thereof imported into the United States under such section or any finished product made from such article or portion, except for export in accordance with section 381(e) or 382 of this title, or with section 262(h) of title 42; or the failure to so export or to destroy such an article or portions thereof, or such a finished product.

(x) The falsification of a declaration of conformity submitted under section 360d(c) of this title or the failure or refusal to provide data or information requested by the Secretary under paragraph (3) of such section.

(y) In the case of a drug, device, or food—

(1) the submission of a report or recommendation by a person accredited under section 360m of this title that is false or misleading in any material respect;

(2) the disclosure by a person accredited under section 360m of this title of confidential

[2] So in original.

commercial information or any trade secret without the express written consent of the person who submitted such information or secret to such person; or

(3) the receipt by a person accredited under section 360m of this title of a bribe in any form or the doing of any corrupt act by such person associated with a responsibility delegated to such person under this chapter.

(z) Omitted.

(aa) The importation of a prescription drug in violation of section 384 of this title, the falsification of any record required to be maintained or provided to the Secretary under such section, or any other violation of regulations under such section.

(bb) The transfer of an article of food in violation of an order under section 334(h) of this title, or the removal or alteration of any mark or label required by the order to identify the article as detained.

(cc) The importing or offering for import into the United States of an article of food by, with the assistance of, or at the direction of, a person debarred under section 335a(b)(3) of this title.

(dd) The failure to register in accordance with section 350d of this title.

(ee) The importing or offering for import into the United States of an article of food in violation of the requirements under section 381(m) of this title.

(ff) The importing or offering for import into the United States of a drug or device with respect to which there is a failure to comply with a request of the Secretary to submit to the Secretary a statement under section 381(*o*) of this title.

(gg) The knowing failure to comply with paragraph (7)(E) of section 374(g) of this title; the knowing inclusion by a person accredited under paragraph (2) of such section of false information in an inspection report under paragraph (7)(A) of such section; or the knowing failure of such a person to include material facts in such a report.

(hh) The failure by a shipper, carrier by motor vehicle or rail vehicle, receiver, or any other person engaged in the transportation of food to comply with the sanitary transportation practices prescribed by the Secretary under section 350e of this title.

(ii) The falsification of a report of a serious adverse event submitted to a responsible person (as defined under section 379aa or 379aa–1 of this title) or the falsification of a serious adverse event report (as defined under section 379aa or 379aa–1 of this title) submitted to the Secretary.

(jj)(1) The failure to submit the certification required by section 282(j)(5)(B) of title 42, or knowingly submitting a false certification under such section.

(2) The failure to submit clinical trial information required under subsection (j) of section 282 of title 42.

(3) The submission of clinical trial information under subsection (j) of section 282 of title 42 that is false or misleading in any particular under paragraph (5)(D) of such subsection (j).

(kk) The dissemination of a television advertisement without complying with section 353b of this title.

(*ll*) The introduction or delivery for introduction into interstate commerce of any food to which has been added a drug approved under section 355 of this title, a biological product licensed under section 262 of title 42, or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless—

(1) such drug or such biological product was marketed in food before any approval of the drug under section 355 of this title, before licensure of the biological product under such section 262 of title 42, and before any substantial clinical investigations involving the drug or the biological product have been instituted;

(2) the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug or such biological product in the food;

(3) the use of the drug or the biological product in the food is to enhance the safety of the food to which the drug or the biological product is added or applied and not to have independent biological or therapeutic effects on humans, and the use is in conformity with—

(A) a regulation issued under section 348 of this title prescribing conditions of safe use in food;

(B) a regulation listing or affirming conditions under which the use of the drug or the biological product in food is generally recognized as safe;

(C) the conditions of use identified in a notification to the Secretary of a claim of exemption from the premarket approval requirements for food additives based on the notifier's determination that the use of the drug or the biological product in food is generally recognized as safe, provided that the Secretary has not questioned the general recognition of safety determination in a letter to the notifier;

(D) a food contact substance notification that is effective under section 348(h) of this title; or

(E) such drug or biological product had been marketed for smoking cessation prior to September 27, 2007; or

(4) the drug is a new animal drug whose use is not unsafe under section 360b of this title.

(mm) The failure to submit a report or provide a notification required under section 350f(d) of this title.

(nn) The falsification of a report or notification required under section 350f(d) of this title.

(*oo*) The sale of tobacco products in violation of a no-tobacco-sale order issued under section 333(f) of this title.

(pp) The introduction or delivery for introduction into interstate commerce of a tobacco product in violation of section 387k of this title.

(qq)(1) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp (including tax stamp), tag, label, or other identification device upon any tobacco product or container or labeling thereof so as to render such tobacco product a counterfeit tobacco product.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing

any punch, die, plate, stone, or other item that is designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of any of the foregoing upon any tobacco product or container or labeling thereof so as to render such tobacco product a counterfeit tobacco product.

(3) The doing of any act that causes a tobacco product to be a counterfeit tobacco product, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit tobacco product.

(rr) The charitable distribution of tobacco products.

(ss) The failure of a manufacturer or distributor to notify the Attorney General and the Secretary of the Treasury of their knowledge of tobacco products used in illicit trade.

(tt) Making any express or implied statement or representation directed to consumers with respect to a tobacco product, in a label or labeling or through the media or advertising, that either conveys, or misleads or would mislead consumers into believing, that—

(1) the product is approved by the Food and Drug Administration;

(2) the Food and Drug Administration deems the product to be safe for use by consumers;

(3) the product is endorsed by the Food and Drug Administration for use by consumers; or

(4) the product is safe or less harmful by virtue of—

(A) its regulation or inspection by the Food and Drug Administration; or

(B) its compliance with regulatory requirements set by the Food and Drug Administration;

including any such statement or representation rendering the product misbranded under section 387c of this title.

(uu) The operation of a facility that manufactures, processes, packs, or holds food for sale in the United States if the owner, operator, or agent in charge of such facility is not in compliance with section 350g of this title.

(vv) The failure to comply with the requirements under section 350h of this title.

(ww) The failure to comply with section 350i of this title.

(xx) The refusal or failure to follow an order under section 350*l* of this title.

(yy) The knowing and willful failure to comply with the notification requirement under section 350f(h) of this title.

(zz) The importation or offering for importation of a food if the importer (as defined in section 384a of this title) does not have in place a foreign supplier verification program in compliance with such section 384a of this title.

(June 25, 1938, ch. 675, § 301, 52 Stat. 1042; Dec. 22, 1941, ch. 613, § 1, 55 Stat. 851; July 6, 1945, ch. 281, § 1, 59 Stat. 463; Mar. 10, 1947, ch. 16, § 1, 61 Stat. 11; June 24, 1948, ch. 613, § 1, 62 Stat. 582; Mar. 16, 1950, ch. 61, § 3(b), 64 Stat. 20; Aug. 7, 1953, ch. 350, § 2, 67 Stat. 477; Pub. L. 85–929, § 5, Sept. 6, 1958, 72 Stat. 1788; Pub. L. 86–618, title I, §§ 104, 105(a), July 12, 1960, 74 Stat. 403; Pub. L. 87–781, title I, §§ 103(c), 104(e)(1), 106(c), 114(a), title III, § 304, Oct. 10, 1962, 76 Stat. 784, 785, 788, 791, 795; Pub. L. 89–74, §§ 5, 9(c), July 15, 1965, 79 Stat. 232, 235; Pub. L. 90–399, § 103, July 13, 1968, 82 Stat. 352; Pub. L. 90–639, § 2(b), Oct. 24, 1968, 82 Stat. 1361; Pub. L. 91–513, title II, § 701(a), Oct. 27, 1970, 84 Stat. 1281; Pub. L. 92–387, § 4(e), Aug. 16, 1972, 86 Stat. 562; Pub. L. 94–295, §§ 3(b), 4(b)(1), 7(b), May 28, 1976, 90 Stat. 576, 580, 582; Pub. L. 96–359, § 5, Sept. 26, 1980, 94 Stat. 1193; Pub. L. 99–570, title IV, § 4014(b)(2), Oct. 27, 1986, 100 Stat. 3207–120; Pub. L. 100–293, § 7(a), Apr. 22, 1988, 102 Stat. 99; Pub. L. 101–502, § 5(j), Nov. 3, 1990, 104 Stat. 1289; Pub. L. 101–508, title IV, § 4755(c)(2), Nov. 5, 1990, 104 Stat. 1388–210; Pub. L. 102–300, § 3(a)(1), June 16, 1992, 106 Stat. 238; Pub. L. 102–571, title I, § 107(2), (3), Oct. 29, 1992, 106 Stat. 4499; Pub. L. 103–80, § 3(c), Aug. 13, 1993, 107 Stat. 775; Pub. L. 103–396, § 2(b)(1), Oct. 22, 1994, 108 Stat. 4154; Pub. L. 103–417, § 10(b), Oct. 25, 1994, 108 Stat. 4332; Pub. L. 104–134, title II, § 2103, Apr. 26, 1996, 110 Stat. 1321–319; Pub. L. 104–170, title IV, § 403, Aug. 3, 1996, 110 Stat. 1514; Pub. L. 104–250, § 5(d), Oct. 9, 1996, 110 Stat. 3156; Pub. L. 105–115, title I, § 125(a)(2)(A), (C), (b)(2)(B), title II, §§ 204(b), 210(c), title IV, §§ 401(b), 421, Nov. 21, 1997, 111 Stat. 2325, 2336, 2345, 2364, 2380; Pub. L. 106–387, § 1(a) [title VII, § 745(d)(1)], Oct. 28, 2000, 114 Stat. 1549, 1549A–39; Pub. L. 107–188, title III, §§ 303(b), 304(d), 305(b), 306(c), 307(b), 321(b)(2), 322(b), June 12, 2002, 116 Stat. 664, 666, 668, 670, 672, 676, 677; Pub. L. 107–250, title II, § 201(d), Oct. 26, 2002, 116 Stat. 1609; Pub. L. 108–136, div. A, title XVI, § 1603(c), Nov. 24, 2003, 117 Stat. 1690; Pub. L. 108–173, title XI, § 1121(b)(1), Dec. 8, 2003, 117 Stat. 2469; Pub. L. 108–214, § 2(b)(2)(A), Apr. 1, 2004, 118 Stat. 575; Pub. L. 108–282, title I, § 102(b)(5)(C), (D), Aug. 2, 2004, 118 Stat. 902; Pub. L. 109–59, title VII, § 7202(d), (e), Aug. 10, 2005, 119 Stat. 1913; Pub. L. 109–462, §§ 2(c), 3(b), 4(a), Dec. 22, 2006, 120 Stat. 3472, 3475; Pub. L. 110–85, title VIII, § 801(b)(1), title IX, §§ 901(d)(1), 912(a), title X, § 1005(d), Sept. 27, 2007, 121 Stat. 920, 939, 951, 968; Pub. L. 111–31, div. A, title I, § 103(b), June 22, 2009, 123 Stat. 1833; Pub. L. 111–353, title I, §§ 102(d)(1), 103(e), 105(c), 106(d), title II, §§ 204(j)(1), 206(d), 211(b), (c), title III, § 301(b), Jan. 4, 2011, 124 Stat. 3889, 3898, 3904, 3906, 3937, 3943, 3953, 3954.)

REFERENCES IN TEXT

Section 2223 of this title, referred to in par. (e), was in the original ''section 204 of the FDA Food Safety Modernization Act'', meaning section 204 of Pub. L. 111–353, which enacted section 2223 of this title and amended this section and section 381 of this title.

AMENDMENTS

2011—Par. (d). Pub. L. 111–353, § 102(d)(1), inserted ''350d,'' after ''344,''.

Par. (e). Pub. L. 111–353, §§ 204(j)(1), 211(c), substituted ''350f(j)'' for ''350f(g)'' and inserted before period at end ''; or the violation of any recordkeeping requirement under section 2223 of this title (except when such violation is committed by a farm)''.

Par. (uu). Pub. L. 111–353, § 103(e), added par. (uu).

Par. (vv). Pub. L. 111–353, § 105(c), added par. (vv).

Par. (ww). Pub. L. 111–353, § 106(d), added par. (ww).

Par. (xx). Pub. L. 111–353, § 206(d), added par. (xx).

Par. (yy). Pub. L. 111–353, § 211(b), added par. (yy).

Par. (zz). Pub. L. 111–353, § 301(b), added par. (zz).

2009—Pars. (a) to (c). Pub. L. 111–31, § 103(b)(1)–(3), inserted ''tobacco product,'' after ''device,''.

Par. (e). Pub. L. 111–31, § 103(b)(4)(B), which directed substitution of ''379aa–1, 387i, or 387t of this title or the refusal to permit access to'' for ''or 379aa–1 of this title or the refusal to permit access to'', was executed by

making the substitution for ''or 379aa–1 of this title, or the refusal to permit access to'', to reflect the probable intent of Congress.

Pub. L. 111–31, §103(b)(4)(A), struck out period after ''360ccc–1(i)''.

Pars. (g), (h). Pub. L. 111–31, §103(b)(5), (6), inserted ''tobacco product,'' after ''device,''.

Par. (j). Pub. L. 111–31, §103(b)(7), struck out period after ''360ccc–2'' and substituted ''379, 379e, 387d, 387e, 387f, 387g, 387h, 387i, or 387t(b)'' for ''379, or 379e''.

Par. (k). Pub. L. 111–31, §103(b)(8), inserted ''tobacco product,'' after ''device,''.

Par. (p). Pub. L. 111–31, §103(b)(9), added par. (p) and struck out former par. (p) which read as follows: ''The failure to register in accordance with section 360 of this title, the failure to provide any information required by section 360(j) or 360(k) of this title, or the failure to provide a notice required by section 360(j)(2) of this title.''

Par. (q)(1). Pub. L. 111–31, §103(b)(10), added subpar. (1) and struck out former subpar. (1) which read as follows: ''The failure or refusal to (A) comply with any requirement prescribed under section 360h or 360j(g) of this title, (B) furnish any notification or other material or information required by or under section 360i or 360j(g) of this title, or (C) comply with a requirement under section 360*l* of this title.''

Par. (q)(2). Pub. L. 111–31, §103(b)(11), substituted ''device or tobacco product,'' for ''device,''.

Par. (r). Pub. L. 111–31, §103(b)(12), inserted ''or tobacco product'' after ''device'' in two places.

Pars. (*oo*) to (tt). Pub. L. 111–31, §103(b)(13), added pars. (*oo*) to (tt).

2007—Par. (e). Pub. L. 110–85, §1005(d)(1), substituted ''350c, 350f(g),'' for ''350c,'' and ''350c(b), 350f'' for ''350c(b)''.

Par. (jj). Pub. L. 110–85, §801(b)(1), added par. (jj).

Par. (kk). Pub. L. 110–85, §901(d)(1), added par. (kk).

Par. (*ll*). Pub. L. 110–85, §912(a), added par. (*ll*).

Pars. (mm), (nn). Pub. L. 110–85, §1005(d)(2), added pars. (mm) and (nn).

2006—Par. (e). Pub. L. 109–462, §3(b), substituted ''374(a), 379aa, or 379aa–1'' for ''374(a), or 379aa'' and ''360bbb–3, 379aa, or 379aa–1'' for ''360bbb–3, or 379aa''.

Pub. L. 109–462, §2(c), substituted '', 374(a), or 379aa'' for '', or 374(a)'' and '', 360bbb–3, or 379aa'' for '', or 360bbb–3''.

Par. (ii). Pub. L. 109–462, §4(a), added par. (ii).

2005—Par. (e). Pub. L. 109–59, §7202(d), inserted ''350e,'' before ''354,'' in two places.

Par. (hh). Pub. L. 109–59, §7202(e), added par. (hh).

2004—Par. (e). Pub. L. 108–282, §102(b)(5)(C), which directed the substitution of ''360b(a)(4)(C), 360b (j), (*l*) or (m), 360ccc–1(i).'' for ''360b(a)(4)(C), 360b(j), (*l*) or (m)'' was executed by making the substitution for ''360b(a)(4)(C), 360b(j), (*l*), or (m)'', to reflect the probable intent of Congress.

Par. (j). Pub. L. 108–282, §102(b)(5)(D), substituted ''360j, 360ccc, 360ccc–1, 360ccc–2.'' for ''360j''.

Par. (gg). Pub. L. 108–214 amended par. (gg) generally. Prior to amendment, text read as follows: ''The knowing failure of a person accredited under paragraph (2) of section 374(g) of this title to comply with paragraph (7)(E) of such section; the knowing inclusion by such a person of false information in an inspection report under paragraph (7)(A) of such section; or the knowing failure of such a person to include material facts in such a report.''

2003—Par. (d). Pub. L. 108–136 substituted ''section 344, 355, or 360bbb–3'' for ''section 344 or 355''.

Par. (e). Pub. L. 108–136 inserted ''360bbb–3,'' after ''350c, 354,'' and substituted ''360i, or 360bbb–3'' for ''or 360i''.

Par. (aa). Pub. L. 108–173 substituted ''prescription drug in violation of section 384'' for ''covered product in violation of section 384''.

2002—Par. (e). Pub. L. 107–188, §306(c)(1), substituted ''by section 350a, 350c, 354, 373, or 374(a) of this title'' for ''by section 350a, 354, or 373 of this title'' and ''under section 350a, 350c(b)'' for ''under section 350a''.

Par. (j). Pub. L. 107–188, §306(c)(2), inserted ''350c,'' after ''350a,''.

Par. (w). Pub. L. 107–188, §322(b), amended par. (w) generally. Prior to amendment, par. (w) read as follows: ''The making of a knowingly false statement in any record or report required or requested under subparagraph (A) or (B) of section 381(d)(3) of this title, the failure to submit or maintain records as required by sections 381(d)(3)(A) and 381(d)(3)(B) of this title, the release into interstate commerce of any article imported into the United States under section 381(d)(3) of this title or any finished product made from such article (except for export in accordance with section 381(e) or 382 of this title or section 262(h) of title 42), or the failure to export or destroy any component, part or accessory not incorporated into a drug, biological product or device that will be exported in accordance with section 381(e) or 382 of this title or section 262(h) of title 42.''

Par. (bb). Pub. L. 107–188, §303(b), added par. (bb).

Par. (cc). Pub. L. 107–188, §304(d), added par. (cc).

Par. (dd). Pub. L. 107–188, §305(b), added par. (dd).

Par. (ee). Pub. L. 107–188, §307(b), added par. (ee).

Par. (ff). Pub. L. 107–188, §321(b)(2), added par. (ff).

Par. (gg). Pub. L. 107–250 added par. (gg).

2000—Par. (aa). Pub. L. 106–387 added par. (aa).

1997—Par. (e). Pub. L. 105–115, §125(b)(2)(B), struck out ''357(d) or (g),'' after ''355(i) or (k),''.

Par. (i)(1). Pub. L. 105–115, §125(a)(2)(C), struck out '', 356, 357,'' before ''or 379e of this title''.

Par. (j). Pub. L. 105–115, §125(a)(2)(A), struck out ''356, 357,'' before ''360,''.

Par. (*l*). Pub. L. 105–115, §421, struck out par. (*l*) which read as follows: ''The using, on the labeling of any drug or device or in any advertising relating to such drug or device, of any representation or suggestion that approval of an application with respect to such drug or device is in effect under section 355, 360e, or 360j(g) of this title, as the case may be, or that such drug or device complies with the provisions of such section.''

Par. (x). Pub. L. 105–115, §204(b), added par. (x).

Par. (y). Pub. L. 105–115, §210(c), added par. (y).

Par. (z). Pub. L. 105–115, §401(b), temporarily added par. (z) which related to dissemination of information in violation of section 360aaa of this title. See Effective and Termination Dates of 1997 Amendment note below.

1996—Par. (e). Pub. L. 104–250 inserted '', 354,'' before ''or 373 of this title'' and ''354,'' before ''355(i) or (k)''.

Par. (j). Pub. L. 104–170 inserted before period at end of first sentence ''; or the violating of section 346a(i)(2) of this title or any regulation issued under that section.''

Pars. (u) to (w). Pub. L. 104–134 redesignated par. (u) relating to introduction into interstate commerce of unsafe dietary supplement as (v) and added par. (w).

1994—Par. (e). Pub. L. 103–396, §2(b)(1)(A), substituted ''357(d) or (g), 360b(a)(4)(C),'' for ''357(d) or (g),''.

Par. (u). Pub. L. 103–417 added par. (u) relating to introduction into interstate commerce of unsafe dietary supplement.

Pub. L. 103–396, §2(b)(1)(B), added par. (u) relating to failure to comply with regulations or orders of Secretary.

1993—Par. (j). Pub. L. 103–80, §3(c)(1), substituted ''379, or 379e'' for ''379e, or 379''.

Par. (s). Pub. L. 103–80, §3(c)(2), substituted ''350a(e)'' for ''350a(d)''.

1992—Pars. (i)(1), (j). Pub. L. 102–571 substituted ''379e'' for ''376''.

Par. (q)(1)(C). Pub. L. 102–300 added cl. (C).

1990—Par. (e). Pub. L. 101–502 substituted ''or (k)'' for ''or (j)''.

Par. (j). Pub. L. 101–508 inserted at end ''This paragraph does not authorize the withholding of information from either House of Congress or from, to the extent of matter within its jurisdiction, any committee or subcommittee of such committee or any joint committee of Congress or any subcommittee of such joint committee.''

1988—Par. (t). Pub. L. 100–293 added par. (t).

1986—Par. (s). Pub. L. 99–570 amended par. (s) generally. Prior to amendment, par. (s) read as follows: ''The

failure to provide the notice required by section 350a(b) or 350a(c), the failure to make the reports required by section 350a(d)(1)(B), or the failure to meet the requirements prescribed under section 350a(d)(2).''

1980—Par. (e). Pub. L. 96–359, § 5(b), inserted reference to section 350a of this title in two places.

Par. (j). Pub. L. 96–359, § 5(c), inserted reference to section 350a of this title.

Par. (s). Pub. L. 96–359, § 5(a), added par. (s).

1976—Par. (e). Pub. L. 94–295, § 3(b)(2), inserted references to sections 360e(f) and 360i of this title.

Par. (j). Pub. L. 94–295, § 3(b)(3), inserted references to sections 360, 360c, 360d, 360e, 360f, 360h, 360i, 360j, and 379 of this title.

Par. (*l*). Pub. L. 94–295, § 3(b)(4), substituted ''drug or device'' for ''drug'' wherever appearing, and inserted references to sections 360e and 360j(g) of this title.

Par. (p). Pub. L. 94–295, § 4(b)(1), substituted ''section 360(j) or 360(k) of this title,'' for ''section 360(j) of this title,''.

Par. (q). Pub. L. 94–295, § 3(b)(1), added par. (q).

Par. (r). Pub. L. 94–295, § 7(b), added par. (r).

1972—Par. (p). Pub. L. 92–387 added failure to provide information required by section 360(j) of this title, and failure to provide notice required by section 360(j)(2) of this title as prohibited acts.

1970—Par. (q). Pub. L. 91–513 struck out par. (q) which set out penalties for illegal manufacture, sale, disposition, possession and other traffic in stimulant and depressant drugs. See section 801 et seq. of this title.

1968—Par. (e). Pub. L. 90–399, § 103(1), struck out ''or'' before ''357(d) or (g)'' and inserted '', or 360b(j), (*l*), or (m)'' after ''357(d) or (g)''. Amendment striking out ''or'' was executed as described, notwithstanding directory language that ''or'' before ''357,'' be stricken out, to reflect the probable intent of Congress.

Par. (j). Pub. L. 90–399, § 103(2), inserted reference to section 360b of this title.

Par. (q). Pub. L. 90–639 divided cl. (3), which referred simply to possession in violation of section 360a(c) of this title, into subcls. (A) and (B) which refer, respectively, to possession in violation of section 360a(c)(1) of this title and possession in violation of section 360a(c)(2) of this title.

1965—Par. (i). Pub. L. 89–74, § 9(c), designated existing provisions as subpar. (1) and added subpars. (2) and (3).

Par. (q). Pub. L. 89–74, § 5, added par. (q).

1962—Par. (e). Pub. L. 87–781, §§ 103(c), 106(c), prohibited the failure to establish or maintain any record, or make any report, required under sections 355(i) or (j) and 507(d) or (g) of this title, or the refusal to permit access to, or verification or copying of, any such required record.

Par. (*l*). Pub. L. 87–781, § 104(e)(1), inserted ''approval of'' before ''an application'', and substituted ''in effect'' for ''effective''.

Par. (*o*). Pub. L. 87–781, § 114(a), added par. (*o*).

Par. (p). Pub. L. 87–781, § 304, added par. (p).

1960—Par. (i). Pub. L. 86–618, § 105(a), struck out references to sections 346(b), 354, and 364 of this title and inserted reference to section 376 of this title.

Par. (j). Pub. L. 86–618, § 104, inserted reference to section 376 of this title.

1958—Par. (j). Pub. L. 85–929, inserted reference to section 348 of this title.

1953—Par. (n). Act Aug. 7, 1953, added par. (n).

1950—Par. (m). Act Mar. 16, 1950, added par. (m).

1948—Par. (k). Act June 24, 1948, inserted ''(whether or not the first sale)'' so as to make it clear that this subsection is not limited to the case where the act occurs while the article is held for the first sale after interstate shipment, and extended coverage of subsection to acts which result in adulteration.

1947—Par. (j). Act Mar. 10, 1947, inserted reference to sections 356 and 357 of this title.

1945—Par. (i). Act July 6, 1945, inserted reference to section 357 of this title.

1941—Par. (i). Act Dec. 22, 1941, inserted reference to section 356 of this title.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by section 103(e) of Pub. L. 111–353 effective 18 months after Jan. 4, 2011, and applicable to a small business (as defined in the regulations promulgated under section 350g(n) of this title) beginning on the date that is 6 months after the effective date of such regulations and to a very small business (as defined in such regulations) beginning on the date that is 18 months after the effective date of such regulations, see section 103(i) of Pub. L. 111–353, set out as an Effective Date note under section 350g of this title.

Pub. L. 111–353, title III, § 301(d), Jan. 4, 2011, 124 Stat. 3955, provided that: ''The amendments made by this section [enacting section 384a of this title and amending this section and section 381 of this title] shall take effect 2 years after the date of enactment of this Act [Jan. 4, 2011].''

EFFECTIVE DATE OF 2007 AMENDMENT

Pub. L. 110–85, title IX, § 909, Sept. 27, 2007, 121 Stat. 950, provided that:

''(a) EFFECTIVE DATE.—This subtitle [subtitle A (§§ 901–909) of title IX of Pub. L. 110–85, enacting sections 353b and 355–1 of this title, amending this section, sections 333, 352, and 355 of this title, and section 262 of Title 42, The Public Health and Welfare, and enacting provisions set out as notes under sections 352, 355, and 355a of this title] takes effect 180 days after the date of the enactment of this Act [Sept. 27, 2007].

''(b) DRUGS DEEMED TO HAVE RISK EVALUATION AND MITIGATION STRATEGIES.—

''(1) IN GENERAL.—A drug that was approved before the effective date of this Act [probably means ''this subtitle'', see above] is, in accordance with paragraph (2), deemed to have in effect an approved risk evaluation and mitigation strategy under section 505–1 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355–1] (as added by section 901) (referred to in this section as the 'Act') if there are in effect on the effective date of this Act elements to assure safe use—

''(A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or

''(B) otherwise agreed to by the applicant and the Secretary for such drug.

''(2) ELEMENTS OF STRATEGY; ENFORCEMENT.—The approved risk evaluation and mitigation strategy in effect for a drug under paragraph (1)—

''(A) is deemed to consist of the timetable required under section 505–1(d) and any additional elements under subsections (e) and (f) of such section in effect for such drug on the effective date of this Act; and

''(B) is subject to enforcement by the Secretary to the same extent as any other risk evaluation and mitigation strategy under section 505–1 of the Act, except that sections 303(f)(4) and 502(y) and (z) of the Act [21 U.S.C. 333(f)(4), 352(y), (z)] (as added by section 902) shall not apply to such strategy before the Secretary has completed review of, and acted on, the first assessment of such strategy under such section 505–1.

''(3) SUBMISSION.—Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect under paragraph (1) shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505–1 of the Act as if included in such application at the time of submission of the application to the Secretary.''

EFFECTIVE DATE OF 2006 AMENDMENT

Amendment by section 2(c) of Pub. L. 109–462 effective 1 year after Dec. 22, 2006, see section 2(e)(1) of Pub. L. 109–462, set out as a note under section 352 of this title.

Amendment by section 3(b) of Pub. L. 109–462 effective 1 year after Dec. 22, 2006, see section 3(d)(1) of Pub. L. 109–462, set out as a note under section 343 of this title.

Pub. L. 109–462, § 4(b), Dec. 22, 2006, 120 Stat. 3475, provided that: ''The amendment made by this section [amending this section] shall take effect 1 year after the date of enactment of this Act [Dec. 22, 2006].''

EFFECTIVE DATE OF 2005 AMENDMENT

Pub. L. 109–59, title VII, §7204, Aug. 10, 2005, 119 Stat. 1914, provided that: ''This subtitle [subtitle B (§§7201–7204) of title VII of Pub. L. 109–59, enacting section 350e of this title, amending this section, sections 342 and 373 of this title, and section 5701 of Title 49, Transportation, omitting sections 5702 to 5714 of Title 49, and enacting provisions set out as a note under section 301 of this title] takes effect on October 1, 2005.''

EFFECTIVE DATE OF 2002 AMENDMENT

Pub. L. 107–188, title III, §321(c), June 12, 2002, 116 Stat. 676, provided that: ''The amendments made by this section [amending this section and sections 360 and 381 of this title] take effect upon the expiration of the 180-day period beginning on the date of the enactment of this Act [June 12, 2002].''

Pub. L. 107–188, title III, §322(c), June 12, 2002, 116 Stat. 678, provided that: ''The amendments made by this section [amending this section and section 381 of this title] take effect upon the expiration of the 90-day period beginning on the date of the enactment of this Act [June 12, 2002].''

EFFECTIVE AND TERMINATION DATES OF 1997 AMENDMENT

Amendment by sections 204, 210, and 421 of Pub. L. 105–115 effective 90 days after Nov. 21, 1997, except as otherwise provided, see section 501 of Pub. L. 105–115, set out as a note under section 321 of this title.

Amendment by section 401(b) of Pub. L. 105–115 effective 1 year after Nov. 21, 1997, or upon Secretary's issuance of final regulations pursuant to section 401(c) of Pub. L. 105–115, whichever is sooner, and ceases to be effective Sept. 30, 2006, see section 401(d), (e) of Pub. L. 105–115, set out as an Effective and Termination Dates note under former section 360aaa of this title.

EFFECTIVE DATE OF 1994 AMENDMENT

Amendment by Pub. L. 103–396 effective upon adoption of final regulations under section 2(c) of Pub. L. 103–396, set out as a Regulations note under section 360b of this title, see section 2(d) of Pub. L. 103–396, set out as a note under section 360b of this title.

EFFECTIVE DATE OF 1990 AMENDMENT

Section 4755(c)(2) of Pub. L. 101–508 provided that the amendment made by that section is effective as if included in subtitle D of title VI of the Omnibus Budget Reconciliation Act of 1989, Pub. L. 101–239, title VI, §§6601, 6602, Dec. 19, 1989, 103 Stat. 2285, see 42 U.S.C. 300aa–1 note, 300aa–10 note.

EFFECTIVE DATE OF 1988 AMENDMENT

Amendment by Pub. L. 100–293 effective upon expiration of 90 days after Apr. 22, 1988, see section 8(a) of Pub. L. 100–293, set out as a note under section 353 of this title.

EFFECTIVE DATE OF 1972 AMENDMENT

Amendment by Pub. L. 92–387 effective on first day of sixth month beginning after Aug. 16, 1972, see section 5 of Pub. L. 92–387, set out as a note under section 360 of this title.

EFFECTIVE DATE OF 1970 AMENDMENT

Amendment by Pub. L. 91–513 effective on first day of seventh calendar month that begins after Oct. 26, 1970, see section 704 of Pub. L. 91–513, set out as an Effective Date note under section 801 of this title.

EFFECTIVE DATE OF 1968 AMENDMENTS

Amendment by Pub. L. 90–399 effective on first day of thirteenth calendar month after July 13, 1968, see section 108(a) of Pub. L. 90–399, set out as an Effective Date and Transitional Provisions note under section 360b of this title.

Amendment by Pub. L. 90–639 applicable only with respect to violations of this chapter committed after Oct. 24, 1968, see section 6 of Pub. L. 90–639, set out as an Effective Date of 1968 Amendments; Transitional Provisions note under section 321 of this title.

EFFECTIVE DATE OF 1965 AMENDMENT

Amendment by Pub. L. 89–74 effective Feb. 1, 1966, see section 11 of Pub. L. 89–74, set out as a note under section 321 of this title.

EFFECTIVE DATE OF 1962 AMENDMENT

Amendment by sections 103(c) and 106(c) of Pub. L. 87–781 effective on first day of seventh calendar month following Oct. 1962, and amendment by section 104(e)(1) of Pub. L. 87–781 effective Oct. 10, 1962, see section 107 of Pub. L. 87–781, set out as a note under section 321 of this title.

Section 114(b) of Pub. L. 87–781 provided that: ''This section [amending this section] shall take effect on the first day of the seventh calendar month following the month in which this Act is enacted [October 1962].''

EFFECTIVE DATE OF 1960 AMENDMENT

Amendment by Pub. L. 86–618 effective July 12, 1960, subject to provisions of section 203 of Pub. L. 86–618, see section 202 of Pub. L. 86–618, set out as a note under section 379e of this title.

EFFECTIVE DATE OF 1958 AMENDMENT

Amendment by Pub. L. 85–929 effective Sept. 6, 1958, see section 6(a) of Pub. L. 85–929, set out as a note under section 342 of this title.

EFFECTIVE DATE OF 1950 AMENDMENT

Amendment by act Mar. 16, 1950, effective July 1, 1950, see section 7 of that act, set out as an Effective Date note under section 347 of this title.

REGULATIONS

Secretary of Health and Human Services to promulgate regulations to implement amendments made by section 401 of Pub. L. 105–115 not later than 1 year after Nov. 21, 1997, see section 401(c) of Pub. L. 105–115, set out as a note under section 360aaa of this title.

SAVINGS PROVISION

Amendment by Pub. L. 91–513 not to affect or abate any prosecutions for violation of law or any civil seizures or forfeitures and injunctive proceedings commenced prior to the effective date of such amendment, and all administrative proceedings pending before the Bureau of Narcotics and Dangerous Drugs [now the Drug Enforcement Administration] on Oct. 27, 1970, to be continued and brought to final determination in accord with laws and regulations in effect prior to Oct. 27, 1970, see section 702 of Pub. L. 91–513, set out as a note under section 321 of this title.

CONSTRUCTION OF 2011 AMENDMENT

Nothing in amendments by sections 103(e), 105(c), 106(d), 204(j)(1), 211(b), (c), and 301(b) of Pub. L. 111–353 to be construed to apply to certain alcohol-related facilities, see section 2206 of this title.

Nothing in amendments by Pub. L. 111–353 to be construed to alter jurisdiction and authorities established under certain other Acts or in a manner inconsistent with international agreements to which the United States is a party, see sections 2251 and 2252 of this title.

CONSTRUCTION OF 2009 AMENDMENTS

Pub. L. 111–31, div. A, title I, §103(p), June 22, 2009, 123 Stat. 1838, provided that: ''Nothing in this section [amending this section and sections 333, 334, 355, 360m, 372 to 374, 375, 379a, 381, 393, 399, and 679 of this title and enacting provisions set out as notes under sections 333 and 387c of this title] is intended or shall be construed to expand, contract, or otherwise modify or amend the

existing limitations on State government authority over tribal restricted fee or trust lands.''

CONSTRUCTION OF 2002 AMENDMENTS

Pub. L. 107–188, title III, § 315, June 12, 2002, 116 Stat. 675, provided that: ''Nothing in this title [enacting sections 350c, 350d, 398, 399, and 679c of this title, sections 3353, 3354, 8319, and 8320 of Title 7, Agriculture, and section 247b–20 of Title 42, The Public Health and Welfare, amending this section, sections 334, 335a, 342, 343, 360, 372, 374, and 381 of this title, and section 43 of Title 18, Crimes and Criminal Procedure, and enacting provisions set out as notes under this section and sections 341, 350c, 350d, and 381 of this title], or an amendment made by this title, shall be construed to alter the jurisdiction between the Secretaries of Agriculture and of Health and Human Services, under applicable statutes and regulations.''

TRANSFER OF FUNCTIONS

For transfer of functions of Federal Security Administrator to Secretary of Health, Education, and Welfare [now Health and Human Services], and of Food and Drug Administration in the Department of Agriculture to Federal Security Agency, see notes set out under section 321 of this title.

§ 332. Injunction proceedings

(a) Jurisdiction of courts

The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown[1] to restrain violations of section 331 of this title, except paragraphs (h), (i), and (j).

(b) Violation of injunction

In case of violation of an injunction or restraining order issued under this section, which also constitutes a violation of this chapter, trial shall be by the court, or, upon demand of the accused, by a jury.

(June 25, 1938, ch. 675, § 302, 52 Stat. 1043; Pub. L. 87–781, title I, § 103(d), title II, § 201(c), Oct. 10, 1962, 76 Stat. 784, 793; Pub. L. 103–80, § 3(d), Aug. 13, 1993, 107 Stat. 775.)

AMENDMENTS

1993—Subsec. (a). Pub. L. 103–80, § 3(d)(1), struck out '', and subject to the provisions of section 17 (relating to notice to opposite party) of the Act entitled 'An Act to supplement existing laws against unlawful restraints and monopolies, and for other purposes', approved October 15, 1914, as amended (U.S.C., 1934 ed., title 28, sec. 381),'' after ''for cause shown''.

Subsec. (b). Pub. L. 103–80, § 3(d)(2), struck out at end ''Such trial shall be conducted in accordance with the practice and procedure applicable in the case of proceedings subject to the provisions of section 22 of such Act of October 15, 1914, as amended (U.S.C., 1934 ed., title 28, sec. 387).''

1962—Subsec. (a). Pub. L. 87–781, § 103(d), struck out ''(e),'' after ''paragraphs''.

Pub. L. 87–781, § 201(c), struck out ''(f),'' after ''paragraphs''.

EFFECTIVE DATE OF 1962 AMENDMENT

Amendment by section 103(c) of Pub. L. 87–781 effective on first day of seventh calendar month following October 1962, see section 107 of Pub. L. 87–781, set out as a note under section 321 of this title.

Section 203 of title II of Pub. L. 87–781 provided that: ''The amendments made by this title [amending this section and section 374 of this title and enacting provisions set out as notes under sections 321 and 374 of this title] shall take effect on the date of enactment of this Act [Oct. 10, 1962].''

§ 333. Penalties

(a) Violation of section 331 of this title; second violation; intent to defraud or mislead

(1) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

(2) Notwithstanding the provisions of paragraph (1) of this section,[1] if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.

(b) Prescription drug marketing violations

(1) Notwithstanding subsection (a) of this section, any person who violates section 331(t) of this title by—

(A) knowingly importing a drug in violation of section 381(d)(1) of this title,

(B) knowingly selling, purchasing, or trading a drug or drug sample or knowingly offering to sell, purchase, or trade a drug or drug sample, in violation of section 353(c)(1) of this title,

(C) knowingly selling, purchasing, or trading a coupon, knowingly offering to sell, purchase, or trade such a coupon, or knowingly counterfeiting such a coupon, in violation of section 353(c)(2) of this title, or

(D) knowingly distributing drugs in violation of section 353(e)(2)(A) of this title,

shall be imprisoned for not more than 10 years or fined not more than $250,000, or both.

(2) Any manufacturer or distributor who distributes drug samples by means other than the mail or common carrier whose representative, during the course of the representative's employment or association with that manufacturer or distributor, violated section 331(t) of this title because of a violation of section 353(c)(1) of this title or violated any State law prohibiting the sale, purchase, or trade of a drug sample subject to section 353(b) of this title or the offer to sell, purchase, or trade such a drug sample shall, upon conviction of the representative for such violation, be subject to the following civil penalties:

(A) A civil penalty of not more than $50,000 for each of the first two such violations resulting in a conviction of any representative of the manufacturer or distributor in any 10-year period.

(B) A civil penalty of not more than $1,000,000 for each violation resulting in a conviction of any representative after the second conviction in any 10-year period.

For the purposes of this paragraph, multiple convictions of one or more persons arising out of the same event or transaction, or a related series of events or transactions, shall be considered as one violation.

[1] So in original. Probably should be followed by a comma.

[1] So in original. Words ''of this section'' probably should not appear.

FUERST ITTLEMAN DAVID & JOSEPH PL

ADDENDUM 9

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission
for the Protection of Human Subjects
of Biomedical and Behavioral
Research

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission
for the Protection of Human Subjects
of Biomedical and Behavioral
Research

DHEW Publication No. (OS) 78-0012

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 30, 1978

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The identification of basic ethical principles that should underlie the conduct of research involving human subjects, and the development of guidelines to assure that such principles are followed, were topics of studies set forth in the Commission's mandate under Public Law 93-348. This mandate also directs the Commission to submit its report to the President, the Congress, and the Secretary of Health, Education, and Welfare.

Unlike most of the previous reports of the Commission, the Belmont Report does not make specific recommendations for administrative actions by the Secretary of Health, Education, and Welfare. Instead, it is our recommendation that the Belmont Report be adopted in its entirety as a statement of departmental policy on the conduct of research involving human subjects. Publication and dissemination of this policy will provide federal employees, members of Institutional Review Boards and scientific investigators with common points of reference for the analysis of ethical issues in human experimentation. While the principles cannot always be applied so as to resolve beyond dispute particular ethical problems, they provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

The Belmont Report is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center and the monthly Commission's deliberations that have been conducted over the nearly four years of our existence.

We appreciate the opportunity to have worked on this fundamental task in the protection of human research subjects.

Respectfully,

Kenneth J. Ryan, M.D.
Chairman

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 30, 1978

The Honorable Walter F. Mondale
President of the United States Senate
Washington, D.C. 20510

Dear Mr. President:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The identification of basic ethical principles that should underlie the conduct of research involving human subjects, and the development of guidelines to assure that such principles are followed, were topics of studies set forth in the Commission's mandate under Public Law 93-348. This mandate also directs the Commission to submit its report to the President, the Congress, and the Secretary of Health, Education, and Welfare.

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Chairman

National Commission for the Protection of Human Subjects
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Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 30, 1978

The Honorable Thomas P. O Neill, Jr.
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The identification of basic ethical principles that should underlie the conduct of research involving human subjects, and the development of guidelines to assure that such principles are followed, were topics of studies set forth in the Commission's mandate under Public Law 93-348. This mandate also directs the Commission to submit its report to the President, the Congress, and the Secretary of Health, Education, and Welfare.

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Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 30, 1978

Honorable Joseph A. Califano, Jr.
Secretary of Health, Education, and Welfare
Washington, D.C. 20201

Dear Mr. Secretary:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The identification of basic ethical principles that should underlie the conduct of research involving human subjects, and the development of guidelines to assure that such principles are followed, were topics of studies set forth in the Commission's mandate under Public Law 93-348. This mandate also directs the Commission to submit its report to the President, the Congress, and the Secretary of Health, Education, and Welfare.

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Respectfully,

Kenneth J. Ryan, M.D.
Chairman

NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

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B E L M O N T R E P O R T

ETHICAL PRINCIPLES AND GUIDELINES FOR RESEARCH INVOLVING HUMAN SUBJECTS

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crimes Trials, the Nuremberg Code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes* intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement.

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* Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. BOUNDARIES BETWEEN PRACTICE AND RESEARCH

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular

individuals.* By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be

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* Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (*e.g.*, blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (*e.g.*, vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

incorporated into a formal research project.*

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. BASIC ETHICAL PRINCIPLES

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons

Respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The

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* Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show a lack of respect for an autonomous agent is to repudiate that person's considered judgments , to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence

Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to

justify research involving children -- even when individual research subjects are not the direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk withhout immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated

equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemmed as a particularly flagrant injustice. In this country, in the 1940s, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (*e.g.*, welfare patients, particular racial and

ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. APPLICATIONS

Application of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hands of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information.

While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written test of comprehension.

Special provision may need to be made when comprehension is severely limited - for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (*e.g.*, infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occures through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful arrayal of relevent data, including, in some cases,alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is

a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits . The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types

of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of the knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the

research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject - or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number

of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research on to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that a distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (*e.g.*, adults before children) and that some classes of potential subjects (*e.g.*, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of the research. This injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized

may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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