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Bureaucrats vs. Physicians: Have Doctors Been Stripped of Their Power to Determine the Proper Use of Human Growth Hormone in Treating Adult Disease?

Ryan Cronin *

INTRODUCTION

It recently has been suggested that millions of dollars in human growth hormone (hGH) prescriptions are being distributed illegally. Articles appearing in non-legal publications have made claims that hGH may not be prescribed off-label. Further, these articles have presented legal analysis laying out narrow legal parameters within which hGH may be prescribed. In opinion letters, the Food and Drug Administration (FDA) has agreed with this interpretation of hGH regulation. Proponents of hGH in the anti-aging community have responded by challenging the validity of this interpretation. This controversy has left doctors unsure of which hGH treatments are legal.

In an article appearing in the *Journal of the American Medical Association (JAMA)*, the authors purported to address the legalities of prescribing hGH.¹ The article suggested that two specific diagnostic criteria must be met to legally diagnose growth hormone deficiency (GHD) before hGH may be legally prescribed as a

* J.D. (2008), Washington University School of Law; B.A. (2002), Loyola College in Maryland. Special thanks to my parents, Edward and Mary Cronin, as well as Thomas and Mary Greene, Todd Richheimer, and Thomas Garry, Esq. Additional thanks to the staff of the *Washington University Journal of Law & Policy*.

1. Thomas T. Perls, Neil Reisman & S. Jay Olshansky, *Provision or Distribution of Growth Hormone for "Antiaging": Clinical and Legal Issues*, 294 *JAMA*, 2086, 2087 (2005). See also Thomas T. Perls, *Anti-Aging Quackery: Human Growth Hormone and Tricks of the Trade—More Dangerous than Ever*, 59A *J. GERONTOLOGY: BIOLOGICAL SCI.* 682 (2004).

treatment.² However, there is little support in the law to support a requirement for doctors to conduct these tests before diagnosing GHd. Accordingly, the authors only use an obscure letter written by a regulatory review officer at the Department of Health and Human Services as legal support.³

The *JAMA* article, along with a later article appearing in *Brandweek*,⁴ prompted a response from the anti-aging community. Attorney Rick Collins, in a lecture to the 13th Annual International Congress on Anti-Aging Medicine, criticized Dr. Perls' legal analysis in the *JAMA* article.⁵ Mr. Collins addressed the legislative intent behind the provisions of the Food, Drug and Cosmetic Act (FDCA)

2. Perls, *supra* note 1, at 2087. These two criteria are: (1) biochemical diagnosis by means of a subnormal response to the standard growth hormone stimulation test (peak GH, < 5.0 ng/L), and (2) patient must be growth hormone deficiency as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or patients who were GH deficient during childhood. *Id.*

3. Letter from Debi Tran, Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communications, Department of Health and Human Services to Robert L. Garnick, Ph.D., Senior Vice President, Regulatory Affairs, Quality & Corporate Compliance (Aug. 25, 2003) (on file with author). This letter objected to Genetech, Inc.'s dissemination of promotional materials related to certain hGH products. *Id.* The objection was that the company failed to provide risk information in its advertising materials. *Id.* The letter also indicated that approved hGH products (specifically Nutropin and Nutropin AQ) are only approved for use in adults who meet the two on-label diagnostic criteria. *Id.*

4. Jim Edwards, *Bad Medicine*, *Brandweek*, Mar. 20, 2006, available at http://www.brandweek.com/bw/search/article_display.jsp?vnu_content_id=1002199181. This article examined the situation where Pharmecia (now owned by Pfizer) allegedly sold and marketed hGH products for anti-aging purposes. *Id.* The issue in that case was whether "Pharmecia and its marketing department [was] in knowing violation of an established [albeit confusing] law, or were they merely pigeons, bagged by a genuine ignorance of regulations and internal communication failures within the company?" *Id.* Most notably, the article stated that the FDCA

explicitly bans anyone from promoting or selling growth hormone for off-label uses.

Under the law, Genotropin was legally approved only for a narrow range of genetic disorders, most commonly for children with stunted bodies that refuse to grow normally. That market is lucrative-treating one child can cost as much as \$35,000 a year- but also extremely limited; in the U.S., perhaps 150,000 children need growth hormone treatment at any one time.

Id.

5. Rick Collins, Attorney, Collins, McDonald: Gann, P.C., Address at the 13th Annual International Congress on Anti-Aging Medicine: The Legal Front: What's New with hGH and Testosterone Replacement Therapy (Oct. 26, 2005). See <http://www.cmgesq.com>; see also <http://www.rickcollinsonline.com>. Rick Collins is an authority on nutritional supplement law and sports drug defense. He represents such other groups as the International Society of Sports Nutrition and the International Federation of Body Builders. *Id.*

that restricts hGH.⁶ He specifically stated that “any implication that the statute was intended to prohibit hormone replacement in mature, clinically deficient adults is incorrect.”⁷ He went on to state that while the use of hGH for non-medical reasons is illegal, nothing in the statute “explicitly states anything about methods of diagnosis.”⁸

Although it is possible that physicians are using less precise tests to diagnose GHd in adults who show symptoms associated with age-related decline,⁹ there is no statutory language that explicitly restricts physicians from diagnosing GHd as they see fit. Dr. Pearl’s analysis would result in the prescription of hGH being more heavily regulated than actual controlled substances such as anabolic steroids or Oxycontin, both with a recognized potential for abuse.¹⁰ It would be up to Congress to place higher restrictions on hGH if it felt it necessary. Based on the legislative history behind the current laws, Congress has indicated no such intention.¹¹

Part I of this Note examines the legislative history behind the FDCA and explains off-label prescription practices. It will also present studies indicating the benefits and possible negative side effects of hGH. Part II analyzes the legislative intent behind adding hGH to the FDCA in 1990, the appropriate deference to be given to the FDA’s interpretation of the statute, and the policy considerations

6. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–395 (2005).

(W)hoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under 505 [21 U.S.C. § 355] and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, United States Code, or both.

21 USC § 333(e)(1) (2000).

7. Collins, *supra* note 5.

8. *Id.* “The natural aging process is neither a disease nor other recognized medical condition, “anti-aging therapy” is not a valid use for hGH.” *Id.* He further noted that performance enhancement is not a valid use. *Id.*

9. Perls, *supra* note 1, at 2088. The author suggests that doctors are diagnosing growth hormone deficiency in adults by testing IGF-1 levels (a proxy for GH levels) in older adults. *Id.* Perls states that this is not a scientific or legally accepted diagnosis of the disease. *Id.*

10. 21 U.S.C. § 812 (2000). Anabolic steroids are Schedule III drugs which have potential for abuse and dependence, but also have accepted medical uses. *Id.*

11. *See generally* S. 1829, S. REP. NO. 101-433.

surrounding the regulatory scheme for hGH. Part III will suggest guidance to doctors who prescribe hGH under the current laws.

I. THE CONTROVERSY SURROUNDING THE OFF-LABEL PRESCRIPTION OF hGH TO ADULTS

A. *Why hGH Has Become Popular Among “Anti-Aging” Medical Practitioners*

The FDA approved hGH as a new drug in 1940.¹² In 1990, a study reported the beneficial effects on body composition of administering hGH to twelve elderly men.¹³ Two recent studies confirmed these findings.¹⁴ The original study was influential in the creation of the anti-aging industry.¹⁵

Although hGH was once expensive and difficult to obtain, scientific advances have made the hGH supply virtually unlimited.¹⁶ Now, the distribution of hGH has grown into a multimillion-dollar anti-aging industry.¹⁷ It has been estimated that as much as 30% of

12. Letter from Michael A. Chappell, Dist. Director, Dallas District Office, Dep't of Health and Human Servs., to Tony Stires, Global Internet Alliance (Feb. 18, 2004) (on file with author). Prior to its approval as a new drug in 1940, growth hormone was neither marketed as a dietary supplement, nor as a food. *Id.* “Therefore, growth hormone is excluded from the definition of a dietary supplement.” *Id.*

13. Mary Lee Vance, *Can Growth Hormone Prevent Aging?*, 349 *NEW ENG. J. MED.*, 779, 779 (2003) (citing D. Rudman et al., *Effects of Human Growth Hormone in Men Over 60 Years Old*, 323 *NEW ENG. J. MED.* 1, 1–6 (1990)). Twelve men between the ages of 61 and 81 who had IGF-1 levels lower than those found in normal young men took growth hormone for six months. *Id.* This test showed an increase in lean body mass, decrease in adipose mass, and an increase in lumbar spine density. *Id.*

14. Vance, *supra* note 13, at 779 citing (MR Blackman et al., *Growth Hormone and Sex Steroid Administration in Healthy Aged Women and Men: A Randomized Controlled Trial*, 288 *JAMA* 2282–92 (2002); MA Papadakis et al., *Growth Hormone Replacement in Older Men Improves Body Composition But Not Functional Ability*, 124 *ANN. INTERN. MED.* 708–16 (1996)).

15. Vance, *supra* note 13, at 779.

16. Jeffrey Hedges, *The Anabolic Steroids Act: Bad Medicine for the Elderly*, 5 *ELDER. L.J.* 293, 300–01 (1997). “Originally hGH was difficult and expensive to obtain because it had to be extracted from the pituitary glands of cadavers. With the advent of synthetic replication, the supply of hGH is no longer limited.” *Id.*

17. Perls, *supra* note 1, at 2086. “Worldwide annual sales of GH are estimated to be \$1.5 to \$2 billion.” *Id.* It has been suggested that 30% of these prescriptions in the United States are for off-label uses. *Id.* It has further been estimated that “212,921 new and refill GH prescriptions were filled by retail and mail service pharmacies in 2004. . . . These prescriptions

the hGH prescriptions in the United States are for uses not approved by the FDA.¹⁸ In 2004 alone, the United States government estimated that between 25,000 and 30,000 older individuals were treated with hGH for anti-aging.¹⁹

B. History of Off-Label Prescriptions

When a manufacturer applies for approval of a new prescription drug, the manufacturer must submit proposed labeling to the FDA.²⁰ This labeling, if approved, becomes the package insert that accompanies the drug itself when it is prescribed.²¹ Drugs prescribed for applications not on the insert, and therefore, approved by the FDA, are referred to as “off-label.”²² Once a drug is approved for one purpose, physicians are free to prescribe it off-label.²³ Estimates vary, but at least half of all prescriptions in the United States are off-label.²⁴

Physicians are free to prescribe drugs for both on- and off-label uses.²⁵ Many off-label uses are widely known and often widely

generated total sales of \$622 million. . . . of these GH prescriptions, 74% were for individuals aged 20 years and older and 43.7% were for individuals aged 40 to 59 years.” *Id.* It is worth noting that in 2002 an estimated 100,000 others obtained hGH without a prescription. *Id.* See also Vance, *supra* note 13.

18. Perls, *supra* note 1. A larger problem exists in the distribution and marketing of hGH over the internet. *Id.* Many web sites boast the anti-aging benefits of hGH and misrepresent the potential side effects. *Id.* Further, in many cases hGH has been distributed over the internet without the required physician supervision. *Id.*

19. *Id.*

20. Kaspar J. Stoffelmayr, *Products Liability and “Off-Label” Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 276 (1996).

21. *Id.*

22. *Id.*

23. Maxwell J. Mehlman, Elizabeth Banger & Matthew M. Wright, *Health Law Symposium: Doping in Sports and the Use of State Power*, 50 ST. LOUIS L.J. 15, 56 (2005).

24. *Id.* See also Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181 (1999); see also Stoffelmayr, *supra* note 20.

25. 59 Fed. Reg. 59, 820, 59, 821 (Nov. 18, 1994). “Once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling.” *Id.* The publication further stated “‘unapproved’ or, more precisely, ‘unlabeled’ uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature Valid new uses for drugs already on the market

recommended within the medical profession.²⁶ Manufacturers, due to the extreme time and financial cost of FDA approval, do not always seek approval for these “off-label” uses.²⁷ Further, a company’s patent will often run out before it can receive the financial gain necessary for the investment.²⁸ As a result, there is often no incentive for companies to seek FDA approval for every off-label use of their drugs.²⁹ The result is that an off-label drug might still be the best and most reliable treatment for a patient.³⁰

C. The Controlled Substances Act

In addition to prescription drugs being regulated by the FDA, some drugs are also regulated under the Controlled Substances Act (CSA).³¹ FDA approved drugs simultaneously regulated under the

are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations.” *Id.*

26. Stoffelmayr, *supra* note 20, at 277.

27. *Id.*

28. *Id.* “If an off-label use is already well known among physicians, adding it to the label would likely have little effect on sales. Additionally, since less than the full life of a drug’s patent usually remains when off-label uses become known, it is harder for a drug manufacturer to recover its investment in having an off-label use approved than it is to recover the initial investment in having the drug approved for its original use.” *Id.*

29. *Id.*

30. *Id.* at 278. An officer of the American Medical Association has stated that “in some cases, if you didn’t use the drug in the off-label way, you’d be guilty of malpractice.” *Id.* See also James O’Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 298 (2003). This is particularly true in the case of rare disease. *Id.* Off-label prescriptions make up 80–90% of drugs used to treat rare disease. *Id.* Financially, it would not make sense for manufacturers to invest in seeking FDA approval for a treatment that is rarely used. *Id.* However, in the absence of off-label applications, patients with rare diseases could be left without treatment options. *Id.*

31. Controlled Substances Act, 21 U.S.C. §§ 801–971 (2000). See also Congressional Research Service, *Gonzales v. Oregon: Physician-Assisted Suicide and the Controlled Substances Act* (Oct. 18, 2005).

Congress enacted the CSA as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. The purpose of the CSA is to regulate the use of controlled substances for legitimate medical purposes and to prevent these substances from being diverted for illegal manufacture, distribution and use. Controlled substances are categorized into five schedules, ranging from Schedule I substances that have no currently accepted medical use in treatment and can be used in very limited circumstances, to substances in Schedules II, III, IV, and V that have recognized

CSA are classified as schedule II, III, IV, and V drugs.³² In 1990, Congress classified anabolic steroids as a schedule III drug.³³ As with all schedule III drugs, physicians can only prescribe steroids for treatment of a disease or other recognized medical condition.³⁴

In 1990, Congress placed anabolic steroids under the Controlled Substances Act.³⁵ This was done in response to the growing problem of the use of anabolic steroids for performance enhancement by athletes.³⁶ In the two Senate hearings leading up to the bill's passage; athletes, coaches, administrators, sports medicine experts, and doctors testified to the widespread use of steroids in sports and to the resulting side effects.³⁷ The purpose of this legislation was to "further restrict the use of steroids," thus increasing penalties for steroid trafficking to match penalties for selling cocaine and other dangerous drugs.³⁸ In the same legislation, Congress placed hGH under the

medical uses and may be manufactured, distributed and used in accordance with the CSA.

Id.

32. 21 U.S.C. § 812(b). Schedule I drugs such as marijuana are deemed to have no medical uses. *Id.*

33. 21 U.S.C. § 812 (2000). The criteria for classification as a Schedule III drug:

(A) The Drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

21 U.S.C. § 812(b)(3).

34. 21 U.S.C. § 333 (2002).

35. Anabolic Steroid Control Act of 1990, 21 U.S.C. § 812 (2000).

36. S. 1829, S. REP. NO. 101-433, at 2-4 (1989). "The committee held 2 full days of hearings on the problem of steroid abuse, focusing on the problem of steroid abuse in amateur and professional sports." *Id.* "Steroid abuse has become a major drug abuse problem in America. As many as 1 million Americans or more have used or are currently using steroids for non-medical purposes, primarily to increase athletic performance and improve physical appearance." *Id.* See also Jeffrey A. Black, *The Anabolic Steroids Control Act of 1990: A Need for Change*, 97 DICK. L. REV. 131, 138 (1992) (stating "In response to the public's growing concern over the use of anabolic-androgenic steroids for nonmedical purposes, Congress enacted the Anabolic Steroids Control Act of 1990."). *Id.*

37. Report 1, *supra* note 36.

38. *Id.* at 1.

The bill would crack down on illegal steroid use in four ways: (1) it would increase steroid trafficking penalties to match the penalties for selling cocaine and other dangerous drugs; (2) it would impose tight record-keeping and production control regulations to prevent the diversion of legally produced steroids into the illicit market;

Food, Drug and Cosmetic Act, the act which formerly regulated anabolic steroids.³⁹

D. Federal hGH Regulation

Originally written to regulate anabolic steroids, the Food, Drug and Cosmetic Act (FDCA) now regulates hGH.⁴⁰ As part of the 1990 legislation increasing steroid regulation, Congress moved hGH onto the FDCA, filling the void left when anabolic steroids were moved from the FDCA to the CSA.⁴¹ The CSA expressly exempts hGH from its reach.⁴²

There was widespread concern in the medical community that hGH would not be treated differently than anabolic steroids.⁴³ Dr. Louis Underwood, speaking on behalf of the pediatric Endocrine

(3) it would give the Drug Enforcement Administration the authority and responsibility to investigate violations involving the illegal production, distribution, or possession with intent to distribute steroids; and (4) the bill would require U.S. demand reduction agencies to incorporate steroids in all federally supported drug abuse prevention, education, and treatment programs.

Id.

39. *Supra* note 35, at sec. 1904. "This legislation would also amend the Food, Drug, and Cosmetic Act to restrict the illegal distribution of human growth hormone which is chemically distinct from steroids." *Id.* See also Collins, *supra* note 5.

40. *Supra* note 39.

41. *Id.*

42. *Id.* at 13. "Section 101(b) creates a new subsection (41) of section 102 of the Controlled Substances Act (21 U.S.C. § 802), which provides a new definition for "anabolic steroids." *Id.*

To be classified as an anabolic steroid, and [sic] drug must be both chemically and pharmacologically related to the male hormone testosterone, and the drug must promote or purport to purport muscle growth. Section 101(b) contains a list of 27 chemicals that are to be considered anabolic steroids under the Controlled Substances Act. The list, however, is not exclusive. Any drug that meets the general definition is [sic] paragraph (A) of the new subsection (41), except human growth hormone and subject to the exemptions specified in section 102 of the bill, shall be considered an anabolic steroid.

Id.

43. *Abuse of Steroids in Amateur and Professional Athletics: Hearing Before the Subcomm. on Crime, of the H. Comm. on the Judiciary*, 101th Cong. 81 (1990) (statement of Louis E. Underwood, M.D., Professor of Pediatrics, University of North Carolina at Chapel Hill).

Society of North America,⁴⁴ opined that hGH should not be “tarred by the same brush used for anabolic steroids.”⁴⁵ Dr. Underwood stressed the differences between anabolic steroids and hGH stating, in part, that the side effects of hGH are much less, hGH has not been shown as an effective performance enhancer, and it is produced in the same form in the body whereas anabolic steroids are not.⁴⁶ Dr. Underwood believed that placing hGH under the CSA would have adverse effects on research being done into other uses of hGH.⁴⁷ As a result of these concerns, Congress treated hGH differently by placing

44. *Id.* The Lawson Wilkins Pediatric Endocrine Society has “approximately 600 physicians who care for children with endocrine diseases and disorders of growth. . . . this group prescribes most of the growth hormone used in the United States.” *Id.*

45. *Id.* Dr. Underwood expressed concern that the scheduling of hGH with anabolic steroids could have a severe impact on patients and “investigative” efforts into the beneficial uses of hGH. *Id.*

46. *Id.* at 82.

With the exception of testosterone, the anabolic steroids are each different from substances produced by the body. In this sense they should be considered to be drugs. On the other hand, the growth hormones that we use therapeutically in short children are either identical to or virtually identical to the normal growth hormone made by the body. Anabolic steroids promote increase in muscle mass and aggressiveness. They can also cause sterility and a variety of different side effects that you have heard about here today. Growth hormone, on the other hand, has very few undesirable side effects, and in the 25 years we have used it in the treatment of short children, it has had amazingly few adverse effects. Unlike steroids, overtreatment with growth hormone has never been reported. I would like to emphasize that. I know of no instance in which it has been shown that therapeutic use of growth hormone has resulted in an overtreatment phenomenon. . . .

Growth hormone doesn't cause aggressive behavior, as we see with anabolic steroids. It doesn't cause the psychological dependency that I believe we will hear about shortly. Growth hormone has entirely different mechanisms of metabolism than anabolic steroids, thereby not allowing it to build up in the body as in the case of anabolic steroids.

Id.

47. *Id.* Dr. Underwood specified four specific possible adverse effects of the failure to uncouple growth hormone from anabolic steroids. *Id.* First is the “adverse psychological effect on the small children that receive growth hormone to grow.” *Id.* Children who take hGH would feel badly and be teased for taking a controlled substance. Second is the concern that “scheduling growth hormone along with steroids will create inconvenience for most patients.” *Id.* Third is the concern that there will be a “likely disruption in supply to patients who receive free growth hormone from the manufacturer.” *Id.* Increased restrictions would likely discourage pediatric endocrinologists from participating in the free growth hormone program. *Id.* And lastly, Dr. Underwood addressed the concern that making hGH a controlled substance would likely place quotas on production, leaving unavailable the free, residual hGH relied on by researchers. *Id.*

it under the less restrictive statute formerly regulating anabolic steroids, as opposed to scheduling hGH under the more restrictive CSA.⁴⁸ The following is resulting provision of the FDCA:

Whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under Section 355 of this title and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, or both.⁴⁹

This language was added at the end of congressional deliberations over the Crime Control Act of 1990, leaving no legislative history to indicate exactly what Congress intended.⁵⁰

The FDCA placed authority for its enforcement on the Drug Enforcement Agency (DEA).⁵¹ The FDCA authorizes the DEA to investigate misuse of hGH.⁵² Further, the Department of Justice has found that in order to prosecute a physician under the FDCA for illegal distribution of hGH, the evidence must include proof that the physician is a drug dealer.⁵³

48. 21 U.S.C. § 812.

49. 21 U.S.C. § 333(e).

50. Maxwell J. Mehlman, Elizabeth Banger, & Matthew M. Wright, *Health Law Symposium: Doping in Sports and the Use of State Power*, 50 ST. LOUIS U. L.J. 15, 56 (2005).

51. 21 U.S.C. § 333(e). “The Drug Enforcement Administration is authorized to investigate offenses punishable by this subsection.” *Id.*

52. *Id.*

53. U.S. DEP’T OF JUSTICE, CIVIL RESOURCE MANUAL 19, HUMAN GROWTH HORMONE/ STEROIDS STATUTORY OVERVIEW (1998).

Prosecuting a physician brings other considerations into play. Because section 333(f)(1) allows physicians to distribute human growth hormone in connection with either (1) treatment of a disease or (2) other recognized medical condition[s] which [have] been authorized by the Secretary of Health and Human Services, additional evidence is necessary to prove that a physician is a drug dealer. Obtaining such evidence can be difficult. Consideration should be given to attempting “controlled buys” using undercover agents or informants. Both search warrants and grand jury subpoenas for the physician’s medical files will often need to be utilized. Of course, in so doing, care must be given to protect the bona fide privacy interests of any legitimate patients the physician might.

Id.

E. hGH Approved for Use in Adults

In 1996, the FDA approved a new condition, adult GHd, for which hGH could be prescribed.⁵⁴ This signified the first time that hGH could legally be given to adults.⁵⁵ This created confusion as to what the FDA now permitted, and confused the application of the 1990 law which is still in effect.⁵⁶ However, the FDA has taken a strict view of the law's application and asserts that a physician who prescribes hGH for an unauthorized use violates federal law.⁵⁷

Based on its interpretation of the statute, the FDA would read the statutory language to imply that physicians cannot prescribe hGH off-label.⁵⁸ However, if this interpretation is applied it would "constitute an unprecedented intrusion into physicians' prescribing authority."⁵⁹ "This language was added at the end of congressional deliberations over the Crime Control Act of 1990 and there is absolutely no legislative history to explain what Congress intended."⁶⁰

According to the Department of Justice, the FDCA is read as allowing physicians to "distribute human growth hormone in connection with either (1) treatment of a disease *or* (2) other recognized medical condition which has been authorized by the Secretary of Health and Human Services"⁶¹ The Department of

54. FDA Drug Approvals for August 1996, <http://www.fda.gov/cder/da/da896.htm> (on August 1, 1996, the FDA approved an application from Eli Lilly and Co. for Humatrope, the first product of human growth hormone approved to treat growth hormone deficiency in adults.) See also Edwards, *supra* note 4. "A classic case of AGHD would be a growth-deficient child entering adulthood or a cancer patient whose glands have been crippled by radiation therapy." *Id.*

55. Edwards, *supra* note 4.

In 1996 . . . the FDA changed the rules slightly, by approving a new diagnosis under which growth hormone could be administered: adult growth hormone deficiency. A classic case of AGHD would be a growth-deficient child entering adulthood or a cancer patient whose glands have been crippled by radiation therapy. The new approval still did not cover anti-aging, but an important door had been opened: For the first time growth hormone could be legally given to adults.

Id.

56. *Id.*

57. *Id.* See also Perls et al., *supra* note 1; see also Collins, *supra* note 5.

58. Mehlman et al., *supra* note 50.

59. *Id.*

60. *Id.*

61. UNITED STATES DEPARTMENT OF JUSTICE, CIVIL RESOURCE MANUAL 19, HUMAN

Justice apparently believes, as evidenced by its disjunctive interpretation of “or” in the statute, that the “treatment of a disease” does not have to be approved by the Secretary of Health and Human Services.⁶² Under this interpretation, the restriction would only apply to “other recognized medical conditions.”⁶³

F. *Gonzales v. Oregon and Administrative Deference*

As recently as 2006, the Supreme Court has prevented the federal government, specifically the Attorney General, from making medical policy decisions absent Congressional intent.⁶⁴ In *Gonzales*, a patient was prescribed a drug which fell under the CSA.⁶⁵ This drug was prescribed as a means for carrying out physician-assisted suicide, legal in the state of Oregon.⁶⁶ The court examined the legislative history behind the CSA and determined that Congress intended the CSA to prevent drug abuse by requiring a physician’s prescription for Schedule II drugs.⁶⁷ Nothing in that act prevented doctors from prescribing drugs for medical practices which are legal.⁶⁸

GROWTH HORMONE/ STEROIDS STATUTORY OVERVIEW (1998) (emphasis added).

62. *Id.*

63. *Id.*

64. *Gonzales v. Oregon*, 546 U.S. 243 (2006).

65. *Id.* at 243. The State of Oregon along with other plaintiffs brought an action seeking relief that would prevent the federal enforcement of the United States Attorney General’s interpretive rule which would have physicians who assist patients with suicide pursuant to the Oregon Death With Dignity Act (ODWDA) would be violating the CSA. *Id.* at 243–44.

66. *Id.* at 243.

In 1994, Oregon became the first State to legalize assisted suicide when voters approved a ballot measure enacting the Oregon Death With Dignity Act (ODWDA). . . . ODWA exempts from civil or criminal liability state-licensed physicians who, in compliance with the specific safeguards in ODWA, dispense or prescribe a lethal dose of drugs upon the request of a terminally ill patient. . . .

The drugs Oregon physicians prescribe under ODWDA are regulated under a federal statute, the Controlled Substances Act (CSA). . . . The CSA allows these particular drugs to be available only by a written prescription from a registered physician. . . .

Id. A November 9, 2001 Interpretive Rule issued by the Attorney General addresses the implementation and enforcement of the CSA with respect to ODWDA. It determines that using controlled substances to assist suicide is not a legitimate medical practice and that dispensing or prescribing them for the purpose is unlawful under the CSA. *Id.* at 249.

67. Controlled Substances Act, 21 U.S.C. §§ 801–971.

68. 21 U.S.C. § 801a (2000).

The Court in *Gonzales* also noted the deference to be given to an administrative interpretation of an ambiguous statute.⁶⁹ The agency is given “substantial deference . . . when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and the agency interpretation claiming deference was promulgated in the exercise of that authority.”⁷⁰ The Court further noted that when an agency interpretation does not meet the requirements for substantial deference it is only “entitled to respect . . . to the extent that it has the power to persuade.”⁷¹

In an earlier decision, the Supreme Court specifically addressed the level of deference to be given to an opinion letter written by an administrative agency.⁷² The Court stated that “interpretations

69. *Gonzales*, 546 U.S. at 247.

70. *Id.* See also *Chevron U.S.A. Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 842–45. In *Chevron*, the Court addressed the level of deference to be given to the EPA’s definition of “source” under the Clean Air Act. *Id.* at 840. The Court upheld the EPA’s interpretation and developed a two-part analysis: First it must be determined whether a statute permits or forbids an agency’s interpretation, and second, if a statute is not clear on step one, the court decides whether the agency’s interpretation of a statute is reasonable or permissible. *Id.* If an agency’s interpretation is reasonable, then the court will defer to the agency’s reading of the statute. *Id.*

71. *Id.* See also *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944):

There is no statutory provision as to what, if any, deference courts should pay to the Administrator’s conclusions. And, while we have given them notice, we have had no occasion to try to prescribe their influence. The rulings of this Administrator are not reached as a result of hearing adversary proceedings in which he finds facts from evidence and reaches conclusions of law from findings of fact. They are not, of course, conclusive, even in the cases with which they directly deal, much less in those to which they apply only by analogy. They do not constitute an interpretation of the Act or a standard for judging factual situations which binds a district court’s processes, as an authoritative pronouncement of a higher court might do. But the Administrator’s policies are made in pursuance of official duty, based upon more specialized experience and broader investigations and information than is likely to come to a judge in a particular case. They do determine the policy which will guide applications for enforcement *140 by injunction on behalf of the Government. Good administration of the Act and good judicial administration alike require that the standards of public enforcement and those for determining private rights shall be at variance only where justified by very good reasons. The fact that the Administrator’s policies and standards are not reached by trial in adversary form does not mean that they are not entitled to respect. This Court has long given considerable and in some cases decisive weight to Treasury Decisions and to interpretative regulations of the Treasury and of other bodies that were not of adversary origin.

Id.

72. *Christensen v. Harris County*, 529 U.S. 576, 587 (2000). The Court in *Christensen* determined the proper level of deference to be given to an opinion letter written by the

contained in . . . opinion letters are entitled to respect under [its] decision in *Skidmore v. Swift and Co.* but only to the extent that those letters have the power to persuade.”⁷³

G. Proponents of the Strict Interpretation of the FDCA

Recent articles have suggested that millions of dollars of hGH are being prescribed illegally.⁷⁴ One purpose of these articles was to address legal issues surrounding the prescription of hGH by doctors to adult patients who they have diagnosed as growth hormone deficient.⁷⁵ It was stated in the *JAMA* article that “off-label” uses of hGH are illegal.⁷⁶ In making this assertion, the authors cite only the FDCA itself and an obscure warning letter written by the FDA in 2004.⁷⁷

Jim Edwards, in an article published in *Brandweek*, claimed that the 1990 law “explicitly bans anyone from promoting or selling growth hormone for off-label uses.”⁷⁸ In the same article, Mr. Edwards asserts that the 1990 law is “so confusing that even seasoned drug marketers are in the dark about what it actually allows and prohibits.”⁷⁹

Accordingly, it is possible—and troubling to these authors—that someone who wants hGH, but does not want to purchase from a “dubious seller” on the internet, can try to get his doctor to prescribe it.⁸⁰ It has been suggested that some of these doctors are measuring

administrator of the United States Department of Labor’s Wage and Hour Division interpreting the Fair Labor Standards Act (FLSA). *Id.* at 580.

73. *Id.* at 587. The Court found the administrator’s opinion letter unpersuasive.

74. See Perls, *supra* note 1, at 2088; Edwards, *supra* note 4.

75. Perls, *supra* note 1, at 2086.

76. *Id.* at 2089. “[C]urrent law explicitly prohibits the distribution of GH except for clearly and narrowly defined indications. Distribution for other uses, or off-label use, such as for anti-aging, age-related conditions and enhancing athletic performance are illegal.” *Id.*

77. *Id.* at 2086. See also FDA Warning letter Chappell MA. to Tony Stires, Global Internet Alliance (Feb. 18, 2004), available at: http://www.fda.gov/foi/warning_letters/g4543d.htm.

78. Edwards, *supra* note 4.

79. *Id.*

80. *Id.*

IGF-1 levels instead of applying the two “on-label” diagnostic criteria.⁸¹

When the IGF-1 levels are lower than those in young adults, doctors are mistakenly diagnosing growth hormone deficiency in adults.⁸² It is estimated that 50,000 adults in the United States are growth hormone deficient, many of whom are not treated with hGH.⁸³ Further, only 1 out of 10,000 patients meet the on-label diagnostic criteria.⁸⁴ This number compared with the over 200,000 prescriptions written each year suggests that many doctors are using less precise means, perhaps testing IGF-1 levels, to diagnose adult growth hormone deficiency.⁸⁵ A prescription based on this type of diagnosis would be off-label.

In both articles, Dr. Perls supports two specific diagnostic criteria that, in his opinion, must be met before hGH is legally prescribed to treat growth hormone deficiency in adults.⁸⁶ These two criteria are

81. Perls, *supra* note 1, at 2088. IGF-1 levels are a proxy for growth hormone levels. *See also* Angela Gentili and Robert A Adler, *Growth Hormone Replacement in Older Men*, available at <http://www.emedicine.com/med/topic3178.htm> (last updated July 15, 2005).

The decrease in lean body mass and increase in adipose tissue that occurs with aging has been suggested to be partly due to the age-associated decrease in growth hormone (GH) and insulinlike growth factor-1 (IGF-1), also known as somatomedin C, which is produced by the liver and other tissues in response to GH. This decline in the secretory activity of the GH-IGF-1 axis has been termed somatopause or hyposomatotropism of aging. . . .

GH is released from the anterior pituitary gland in a pulsatile manner. Two hypothalamic hormones control GH secretion: Growth hormone-releasing hormone (GHRH) stimulates GH secretion, and somatostatin inhibits it. The majority of GH secretion occurs at night during slow-wave sleep, when somatostatin release is diminished. . . .

GH stimulates production of IGF-1 in the liver and other tissues. . . . Both GH and IGF-1 have important metabolic actions in several tissues. . . .

A single measurement of plasma GH levels is difficult to interpret because of the pulsatile secretion of GH. Levels of IGF-1 vary but little during the day; therefore, assays of IGF-1 have been used as a better indicator of the status of the GH-IGF-1 axis.

Id.

82. Perls, *supra* note 1, at 2088.

83. *Id.*

84. *Id.*

85. *See* Perls, *supra* note 1.

86. *Id.*

included on many of the FDA approved labels which accompany the drug.⁸⁷ Prescriptions of hGH based on meeting these two criteria are therefore on-label. There is a unanimous consensus that an on-label prescription of hGH is legal.

Dr. Perls uses a letter written by a regulatory officer at the Department of Health and Human Services to a senior officer at Genentech, Inc. as sole support of his contention that these two prescription steps are in fact mandated by law.⁸⁸ The purpose of the letter was to request that Genentech cease its dissemination of promotional materials for Nutropin (a growth hormone) without necessary risk information.⁸⁹ The letter contained a list of the approved uses of hGH, and correctly specified the only “approved” use of hGH in adults.⁹⁰ The letter makes no mention of off-label prescriptions.⁹¹

These two criteria are: (1) biochemical diagnosis by means of a subnormal response to the standard growth hormone stimulation test (peak GF, < 5.0 ng/L), and (2) patient must be growth hormone deficient as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or patients who were GH deficient during childhood.

Id.; see also *infra* note 87.

87. See Perls, *supra* note 1. See also Tran, *infra* note 88. The label accompanying Nutropin products was attached with the letter. *Id.*

88. Letter from Debi Tran, Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communications, Department of Health and Human Services to Robert L. Garnick, Ph.D., Senior Vice President, Regulatory Affairs, Quality & Corporate Compliance (Aug. 25, 2003) (on file with author). This letter objected to Genentech, Inc.’s dissemination of promotional materials related to certain hGH products. *Id.* The objection was that the company failed to provide risk information in its advertising materials. *Id.* The letter also indicated that approved hGH products (specifically Nutropin and Nutropin AQ) are only approved for use in adults who meet the two “on-label” diagnostic criteria. *Id.*

89. *Id.*

Promotional materials are false or misleading if they fail to reveal facts material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials....The promotional panels are misleading because they present the indications and uses for the various formulations for Nutropin but entirely omit important risk information that is critical to the appropriate use of Nutropin.

Id.

90. *Id.*

Nutropin and Nutropin AQ are approved for the following indications” long-term treatment in pediatric patients with growth failure due to lack of adequate endogenous growth hormone (GH) secretion; treatment of growth failure in pediatric patients

Most FDA-approved drugs may be prescribed “off-label,” however, the FDA interprets the FDCA to mandate all prescribing of hGH to be “on-label” (i.e., for an “authorized use”).⁹² The FDA’s strict interpretation of the statute limits hGH prescriptions to legitimate adult growth hormone deficiency when both on-label criteria are met. Prescribing hGH for any other reason, including diseases and medical research, would be prohibited. Even the *Brandweek* article characterizes this position as “an unusually strict view of the 1990 statute.”⁹³

H. Response from the Anti-Aging Community

Rick Collins, in a lecture to the 13th Annual International Congress on Anti-Aging Medicine, stated that the interpretation of

associated with chronic renal insufficiency up to the time of renal transplantation; and long-term treatment of short stature in pediatric patients with Turner syndrome. . . .

Nutropin and Nutropin AQ are also approved for the replacement of endogenous GH in adult patients with GH deficiency who meet two criteria:

(1) biochemical diagnosis of adult GH deficiency by means of a subnormal response to a standard growth hormone stimulation test (peak GH \leq μ /L); and,

(2) adult-onset patients who have adult GH deficiency either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma or childhood-onset patients who were GH deficient during childhood, confirmed as an adult before replacement therapy with Nutropin is started. *Id.*

Nutropin Depot is approved for the following indication: the long-term treatment of growth failure in pediatric patients due to a lack of adequate endogenous GH secretion.

Id.

91. *Id.*

92. *Id.* See also Collins, *supra* note 5.

93. Edwards, *supra* note 4.

Confusion had grown in the industry as to what, exactly, the FDA now permitted. Marketers and doctors knew the drug was approved for adults-enough “of a green light for many in the industry. And so the 1990 law became a distant memory, even though it remains very much in effect.”

Id. The FDA takes an unusually strict view of the 1990 statute. (The) FDA believes that a physician who prescribes, dispenses, and/or administers hGH for an unauthorized use violates federal law. *Id.* Richard Collier, former counsel to the pharmaceutical company Pharmacia doubts the FDA’s position is correct. *Id.* “It may be ill-advised or inappropriate to market off-label but it is permissible for a physician to prescribe off-label.” *Id.*

the restrictions on hGH prescriptions is open to debate.⁹⁴ Collins' presentation, as cautionary as it was explanatory, cited the potential criminal enforcement ramifications of FDA's strict interpretation of the FDCA. However, he suggested that the FDA's strict interpretation of the FDCA is not what Congress intended.⁹⁵ He conceded the problematic wording of the statute, stating that "(t)he law on hGH does (curiously) place greater limitations on hGH prescribing than on controlled substances, including anabolic steroids, which may be prescribed for any legitimate medical purpose."⁹⁶ But Collins notes that nothing in the legislative history suggests such a strict interpretation, citing Congress' intent to curb hGH use as a performance enhancer in athletes but not as off-label prescriptions.⁹⁷

The U.S. Attorney's online Civil Resource Manual states that the law "allows physicians to distribute human growth hormone in connection with either (1) "treatment of a disease" or (2) "other recognized medical condition" which has been authorized by the Secretary of Human Services."⁹⁸ Collins poses the question: "does the division as stated suggest that if the use is to treat a disease, as opposed to treating an 'other . . . condition,' the use need not be authorized by the FDA?"⁹⁹

This interpretation of the statute treats the word "or" as disjunctive. The U.S. Attorney's manual appears to read the statute the same way. Applying the disjunctive interpretation, hGH could be legally prescribed to an adult patient where there is "either, (1) some component of "disease" being legitimately treated (e.g., symptoms, evidence of biochemical deficiency, etc.) or (2) some other "recognized medical condition" and an FDA-approved use."¹⁰⁰

94. Collins, *supra* note 5.

95. *Id.* "[The] FDA's extreme interpretation of the law's restrictions seems to make no sense." *Id.*

96. *Id.*

97. *Id.* "The objective was not to target anti-aging medicine (which had not yet come into existence) or specifically to restrict medical prescribing for disease, but to address the abuse of hGH by athletes to cheat in sports." *Id.*

98. U.S. DEP'T OF JUSTICE, CIVIL RESOURCE MANUAL 19, HUMAN GROWTH HORMONE/ STEROIDS STATUTORY OVERVIEW (1998); *see also* Collins, *supra* note 5.

99. *Id.*

100. *Id.*

Collins argued that there are considerable benefits to this “correct” disjunctive construction of the FDCA.¹⁰¹ Specifically, the disjunctive reading of the FDCA “lets physicians, not bureaucrats, determine what’s best for patients with a disease.”¹⁰²

I. Just How Beneficial or Dangerous Might hGH Be to Adults?

The extent of the potential costs and benefits from the use of hGH are not yet fully known. However, studies have shown both potential positive and negative effects of hGH. While the most commonly known effect of hGH in adults is muscle growth, it is possible that it has many more beneficial effects.

Aging adults experience a variety of ailments that hGH could treat.¹⁰³ For example, hGH has been shown to counteract the weakening of an adult’s immune system to some extent.¹⁰⁴ Second, it has been shown that hGH can be effective in fighting skin cancer.¹⁰⁵ Third, hGH can improve declining brain function in aging adults.¹⁰⁶

101. *Id.*

102. *Id.* Collins adds that at this reading doctors are able to apply the latest research data when appropriate.

103. Elmer M. Cranton, M.D. & William Fryer, *hGH: The Body of Evidence* (adapted from the book ELMER M. CRANTON, M.D. & WILLIAM FRYER, *RESETTING THE CLOCK: 5 ANTI-AGING HORMONES THAT ARE REVOLUTIONIZING THE QUALITY AND LENGTH OF LIFE* (M. & Evans Co. 1996)), available at http://www.drcranton.com/hrt/hGH_Body_of_Evidence.pdf.

104. *Id.*

105. *Id.* at 2.

We already have evidence that growth hormone will indeed stimulate one kind of immunity in people. A study was conducted at the University of New Mexico School of Medicine on older women with low levels of human growth hormone.⁴ The researchers were intrigued by the correlation of two facts. First, that in both animals and humans a deficiency in growth hormone is associated with an impairment in natural killer (NK) cell activity. Second, that a decrease in NK activity occurs naturally with aging. . . .

Recent research indicates that NK cells are designed to sense any cell that is dividing at an abnormally rapid rate—which is the exact characteristic of a cancer. NK cells go directly to such a site of abnormality; attach themselves to the suspect cell; and, acting as judge, jury, and executioner all in one, give it such a walloping dose of chemical toxicity that the offending malignant cell promptly croaks. Immunologists now believe that without these superb and necessary assassins, we would very quickly become statistics on the national cancer charts. Which is exactly what happens to a large percentage of AIDS patients as their natural killer cell counts go down.

Id.

106. *Id.* at 6–7.

Fourth, hGH could be beneficial in treating patients with injuries to the central nervous system.¹⁰⁷ Last, hGH has been shown in recent studies to be effective in combating obesity.¹⁰⁸ While it is unnecessary here to examine all of the possible scientific data supporting beneficial uses of hGH, it is clear that there are many possibilities for the beneficial use of hGH in treating adults.

Members of the Senate and House, encouraged by hGH's safety record, have also supported loosening restrictions on hGH.¹⁰⁹ On February 10, 2006, Senator Orrin Hatch and Congressman Henry Waxman sent a letter to the FDA arguing there "is simply no excuse—scientific, legal, or otherwise—for FDA to continue to delay the release of [guidance documents on the approval requirements for generic hGH versions]," adding that hGH is one of the biologic products with "relatively simple structures with a long history of safe use by millions of people. . . ."¹¹⁰

There have also been indications that hGH could potentially harm adults. One study has shown a possible increase in the risk of prostate cancer when hGH is used in elderly patients.¹¹¹ Another study has shown a dramatic increase in the occurrence of diabetes, carpal

An important discovery of recent years is that growth hormone and its byproduct IGF-1 (somatomedin-C) can also act as nerve growth factors. If they too support the functioning of the central nervous system, then growth hormone's decline may be in part responsible for the mental decline that many people experience with age. Certainly, as you're about to see, replacement of hGH can have startling effects on people with many forms of neurological disorder—not just mental but physical as well.

Id.

107. *Id.* at 7. Edward Chin, M.D. . . . has said with reference to growth hormone that "We have a therapy that can repair systems. Damage to the neurologic system resulting from age or injury can be repaired." *Id.* Chaovanee Aroonsakul, M.D., of the Alzheimer's and Parkinson's Disease Diagnostic and Treatment Center in Naperville, Illinois, has discussed her own successes using growth hormone. *Id.* She has been able to demonstrate the regeneration of nerve cells, restored hormonal balance, and improved functional capacity in patients with Alzheimer's disease, senile dementia, Parkinson's disease, and stroke. *Id.* Dr. Aroonsakul writes that "Further experience with these methods has demonstrated their usefulness for a variety of age-related conditions including osteoporosis, osteoarthritis, sexual dysfunction, lack of stamina, and mental and physical slowing." *Id.*

108. Akihiro Ikeda et al., *Obesity and Insulin Resistance in Human Growth Hormone Transgenic Rats* 139 *ENDOCRINOLOGY* 7, 3057–63 (1998).

109. Collins, *supra* note 5.

110. *Id.*

111. Vance, *supra* note 13, at 779.

tunnel syndrome, edema and arthralgias in patients treated with hGH.¹¹² Another potential risk is that long-term treatment could significantly increase a patient's risk of developing breast cancer.¹¹³ Further, there have also been indications from tests performed on laboratory rodents that hGH might actually reduce life expectancy.¹¹⁴

Some say the physical benefits of hGH may be overvalued. While hGH has been shown to change body composition, it has not been shown to improve function, strength or metabolism in aging adults.¹¹⁵ Further, one study suggests that the positive effects of hGH might be short-lived.¹¹⁶

Skeptics worry that inappropriate prescription of hGH could cause an inefficient allocation of health care resources.¹¹⁷ Growth hormone replacement can cost between \$7,500 and \$10,000 annually.¹¹⁸ It is estimated that one third of the prescriptions of hGH in the United States are for off-label uses which are not approved by the FDA.¹¹⁹ This leads to concerns that inappropriate prescriptions could end up being reimbursed, while the patients most in need will have a harder time being reimbursed because of increased "off-label" prescriptions.¹²⁰ There is also a possible negative impact on third party payers, effectively having them pay the costs for arguably illegal prescriptions.¹²¹

II. THE EFFECT OF FEDERAL REGULATION ON PHYSICIANS' ABILITY TO PRESCRIBE HGH TO ADULTS OFF-LABEL

On its face, the FDCA does not forbid the off-label prescription of hGH to adults. As a result, we face a dangerous situation where

112. *Id.* (citing MR Blackman et al., *Growth Hormone and Sex Steroid Administration in Healthy Aged Women and Men: A Randomized Controlled Trial*, 288 JAMA, 2282–92 (2002)).

113. Perls, *supra* note 1, at 2086.

114. Edwards, *supra* note 4.

115. Vance, *supra* note 13.

116. Perls, *supra* note 1, at 2086 (citing J Verhelst et al., *Two Years of Replacement Therapy in Adults with Growth Hormone Deficiency*, 47 CLINICAL ENDOCRINOLOGY (Ox) 485–94 (1997)).

117. Vance, *supra* note 13, at 780.

118. *Id.* This number was calculated for a patient with GHd.

119. *Id.*

120. *Id.*

121. *Id.*

doctors are unsure whether prescribing hGH, a potentially effective course of treatment for off-label diseases, is illegal. A closer look at the statutory construction, Congressional intent, and policy considerations is necessary to determine whether doctors can legally prescribe hGH off-label.

A. Legislative History Indicates No Congressional Intent to Limit Physicians' Ability to Prescribe hGH Off-Label

In 1990, Congress passed the Anabolic Steroid Control Act which made anabolic steroids a schedule III controlled substance.¹²² The Act also amended the FDCA to restrict illegal distribution of hGH.¹²³ The legislative history makes clear that the 1990 Act was intended to curtail the use of anabolic steroids and hGH as athletic performance enhancers.¹²⁴ Nowhere in the history is there any indication that Congress considered universally outlawing the off-label prescription of hGH.¹²⁵

The Anabolic Steroid Control Act of 1990 attempted to curb the growing problem of steroid abuse in America.¹²⁶ Congress noted that “as many as 1 million Americans or more have used or are currently using steroids for non-medical purposes, primarily to increase athletic performance and improve physical appearance.”¹²⁷ Before the passage of the Act, the Senate Committee on the Judiciary held two full days of hearings which “focus[ed] on the problem of steroid abuse in amateur and professional sports.”¹²⁸ These hearings saw a parade of coaches, athletes, administrators, and doctors who all

122. Pub. L. No. 101-647, Sec. 1902, 104 Stat. 4851 (1990), amending 21 U.S.C. § 812(c) (1981) to include anabolic steroids. *See also* 21 U.S.C. § 802(41)(A).

123. 21 U.S.C. § 333 (e).

124. S. REP. NO. 101-433, at 1; *see also, e.g., Steroids in Amateur and Professional Sports—The Medical and Social Costs of Steroid Abuse: Hearings Before the Senate Comm. on the Judiciary*, 101st Cong. 1st Sess. 736, April 3 and May 9, 1989; *Abuse of Steroids in Amateur and Professional Athletics: Hearings Before the Subcomm. on Crime of the House Comm. on the Judiciary*, 101st Cong., 2d Sess. 92, March 22, 1990; *Hearings on H.R. 4658 Before the Subcomm. on Crime of the House Comm. on the Judiciary*, 101st Cong., 2d Sess. 90, May 17, 1990.

125. *See generally* S. 1829, S. REP. NO. 101-433.

126. *Id.*

127. *Id.*

128. *Id.*

addressed the problem of steroid use by athletes.¹²⁹ This extensive testimony on non-medical performance enhancement, coupled with the absence of testimony concerning medical uses, is the most obvious indication that this legislation was not intended to regulate medical prescriptions of hGH in adults.

A second, and equally compelling indicator of congressional intent, is the illogical outcome that would result from a strict reading of the FDCA. Congress explicitly intended to place stronger restrictions on anabolic steroids in the Control Act.¹³⁰ It accomplished this by making anabolic steroids a controlled substance under the Controlled Substances Act.¹³¹ Simultaneously, Congress inserted hGH into the less restrictive FDCA, the same regulatory classification anabolic steroids had been in.¹³² This distinction made between hGH and anabolic steroids clearly and unambiguously shows congressional intent to regulate anabolic steroids on a stricter level than hGH.

In contrast, proponents of a strict interpretation of the FDCA argue that hGH should be regulated at a higher level than anabolic steroids. Specifically advocating a ban on off-label prescriptions of hGH, regulation of hGH prescriptions would exceed similar regulations of anabolic steroids¹³³ because anabolic steroids, and all other FDA approved schedule III drugs, can be prescribed off-label.¹³⁴

Further, there was significant attention paid to the separation of hGH and anabolic steroids in the new legislation. The testimony of Dr. Underwood before the House Subcommittee on Crime paid particular attention to the vast differences (both in chemical makeup and risks) between hGH and anabolic steroids.¹³⁵ Dr. Underwood

129. *Id.*

130. 21 U.S.C. § 812.

131. *Id.*

132. 21 U.S.C. § 333(e).

133. *Id.*; see also 21 U.S.C § 812(c), and Collins, *supra* note 5.

134. Collins, *supra* note 5.

135. *Hearing on the Abuse of Steroids in Amateur and Professional Athletics*, *supra* note 43.

advocated that hGH not be “tarred by the same brush used for anabolic steroids.”¹³⁶

Congress seems to have agreed with Dr. Underwood as evidenced in the language of the committee report noting that hGH “is chemically distinct from steroids.”¹³⁷ Secondly, as a result of these acknowledged distinctions, Congress declined to go as far as scheduling hGH as a controlled substance, and instead placed it into the less restrictive FDCA.¹³⁸ And third, considering the placement of the hGH provision at the end of the statute, with no guidance as to what Congress intended, it must be assumed that heavy reliance was placed on Dr. Underwood’s testimony.¹³⁹ As such, hGH was intended to be less regulated than anabolic steroids, especially in relation to its medical uses.

B. The Proper Level of Administrative Deference Leaves the FDA’s Interpretation of the FDCA Unpersuasive

The authors of the “Bad Medicine” article failed to cite any compelling legal authority for their strict interpretation of the FDCA. This is further proof that their interpretation is inaccurate.

The authors site an obscure letter written from an officer at the FDA to a drug company that distributes hGH, which interprets the word “or” in the FDCA provision to be read conjunctively.¹⁴⁰ The Supreme Court has held that opinion letters written by federal agencies are valuable only in their ability to persuade, and are not legally binding.¹⁴¹

To the extent that the FDA’s interpretation is persuasive, it is counteracted by the Justice Department’s interpretation of the FDCA in its civil service manual, which reads “or” in the provision of the

136. *Id.*

137. S. 1829, S. REP. NO. 101-433 at 2.

138. 21 U.S.C. § 333(e).

139. *Id.*

140. Perls, *supra* note 1. Reading “or” conjunctively results in the phrase “authorized by the Secretary of Health and Human Services” applying to both “other recognized medical condition” and “treatment of a disease.” *Id.*

141. *Christensen*, 529 U.S. at 587.

FDCA disjunctively.¹⁴² Under *Christensen*, such a manual is granted the same level of deference as an opinion letter from the FDA.¹⁴³

C. Applying the Supreme Court's Decision in Gonzalez v. Oregon to the Interpretation of the Food, Drug and Cosmetic Act

The FDA, like the Attorney General in *Gonzales v. Oregon*, is attempting to reach beyond its power by applying a statute in a way it was not intended.¹⁴⁴ Nothing in the FDCA restricts a doctor from prescribing hGH for medical purposes.¹⁴⁵ Like in *Gonzales v. Oregon*, where the statute was intended to curb drug abuse,¹⁴⁶ the FDCA was intended to curb the use of hGH as a performance enhancer.¹⁴⁷ This is a far cry from the aging adults whom doctors have diagnosed as growth hormone deficient, or some other recognized medical condition.

Further, Congress explicitly authorized the Drug Enforcement Agency (DEA) to enforce the FDCA.¹⁴⁸ The DEA is an arm of the Department of Justice, not the FDA.¹⁴⁹ Because Congress did not delegate authority to the FDA, the FDA is not entitled to “substantial deference.”¹⁵⁰ Instead, like the Attorney General’s interpretation in *Gonzales v. Oregon*, it is entitled to respect only to the extent that it “has it has the power to persuade.”¹⁵¹ And like the Attorney General’s interpretation of the CSA in *Gonzales*, the FDA’s interpretation of

142. Collins, *supra* note 5. Reading “or” disjunctively results in the phrase “approved by the Secretary of Health and Human Services” applying only to “other recognized medical conditions(s)” leaving doctors free to prescribe hGH off-label to treat disease where that treatment was not approved by the Secretary of Health and Human Services. *Id.*

143. *Christensen* 529 U.S. at 587. “Interpretations such as those in opinion letters—like interpretations contained in policy statements, agency manuals, and enforcement guidelines, all of which lack the force of law—do not warrant *Chevron*-style deference.” *Id.* See also *Skidmore*, 323 U.S. at 140.

144. See generally *Gonzales*, 546 U.S. at 247.

145. See generally 21 U.S.C. § 333.

146. *Gonzales*, 546 U.S. at 246.

147. S. 1829, S. REP. NO. 101-433 at 1; see also *Hearing on the Abuse of Steroids in Amateur and Professional Athletics supra* note 44.

148. 21 U.S.C. § 333.

149. Exec. Order No. 11, 727, 38 Fed. Reg. 18,357 (July 6, 1973); see also Department of Justice Organization Chart (2006), available at <http://www.usdoj.gov/dojorg.htm>.

150. 21 U.S.C. § 333; see also *Chevron U.S.A.*, 467 U.S. at 845.

151. *Gonzales v. Oregon*, 546 U.S. at 908; see also *Skidmore*, 323 U.S. at 134, 140.

the FDCA is unpersuasive.¹⁵² For these reasons, the Supreme Court's decision in *Gonzales v. Oregon* strongly supports the conclusion that hGH may be prescribed off-label.

D. Established History of Off-Label Prescriptions Should Apply to hGH

Scientific literature indicates that hGH has enormous potential to treat a broad spectrum of diseases beyond GHd. Further, Dr. Underwood's testimony makes clear that hGH is not as dangerous as controlled performance enhancers such as anabolic steroids.¹⁵³ While it is important that the FDCA be enforced to curb performance enhancers, including hGH, the statute should not be interpreted so strictly as to restrict doctors in treating disease.

First, as is the case with so many other drugs, it may not be cost effective for drug companies to seek approval for other uses for hGH.¹⁵⁴ If applied strictly, the FDCA could prevent countless treatments from being developed. It is in the public interest to prevent undue bureaucratic obstruction to innovation.

Second, a strict application of the FDCA would remove some treatment decisions from the doctor-patient relationship and place them in the hands of bureaucrats.¹⁵⁵ A potentially effective treatment supported by research should be available to patients so long as the drug has been approved by the FDA for some on-label use.

CONCLUSION

Doctors who prescribe hGH off-label for legitimate medical purposes should not face criminal liability for doing so. Unfortunately, opponents of hGH have taken advantage of public concern over performance enhancing drugs to advance their position to hinder off-label uses of hGH.¹⁵⁶ Those that espouse a strict

152. *Gonzales*, 546 U.S. at 909.

153. *Hearing on the Abuse of Steroids in Amateur and Professional Athletics*, *supra* note 44.

154. Stoffelmayr, *supra* note 20, at 277.

155. Collins, *supra* note 5.

156. *Id.* "We have an atmosphere in which positive research findings receive scant

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interpretation of the FDCA provision, including the FDA, base their arguments on legal analysis which is, at best, unsound.

It is certainly foreseeable that doctors unfamiliar with statutory interpretation will become concerned by some of their colleagues' articles and by the FDA's position. It is important that these doctors not change their courses of treatment to avoid criminal liability under the FDCA.

It is more important, however, that Congress speak with a clear voice on hGH regulation. The FDCA's provision regulating hGH is confusing. Congress should pass new legislation which clearly guides doctors. Such legislation must take into consideration public policy implications that come with heavy restrictions on hGH. hGH has the potential to greatly help patients with certain conditions and there is evidence of its potential to help many more. There is also evidence cutting in the other direction. What is clear is that any new legislation must leave room for innovation so that physicians can put hGH to its most beneficial use.

attention, but harsh criticism and negative attacks receive broad dissemination in both the scientific and law press." *Id.*