ORAL ARGUMENT MARCH 1, 2007

CASE NO. 04-5350

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

ABIGAIL ALLIANCE FOR BETTER ACCESS
TO DEVELOPMENTAL DRUGS, *et al.*,
Appellants,

v.

ANDREW C. VON ESCHENBACH, *et al.*,
Appellees.

ON APPEAL FROM THE DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

EN BANC BRIEF OF APPELLANTS

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Dated: December 29, 2006

APPELLANTS' CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES PURSUANT TO D.C. CIR. RULE 28(a)(1)

Parties

The parties are appellants Abigail Alliance for Better Access to Developmental Drugs and the Washington Legal Foundation and appellees Dr. Andrew von Eschenbach, in his official capacity as Commissioner of the Food and Drug Administration, and Michael O. Leavitt, in his official capacity as Secretary of the United States Department of Health and Human Services. Mark B. McClellan was originally a defendant, but was first changed to Lester M. Crawford and now to Andrew C. von Eschenbach by operation of Fed. R. App. P. 43(c)(2).

Disclosure Required by Circuit Rule 26.1

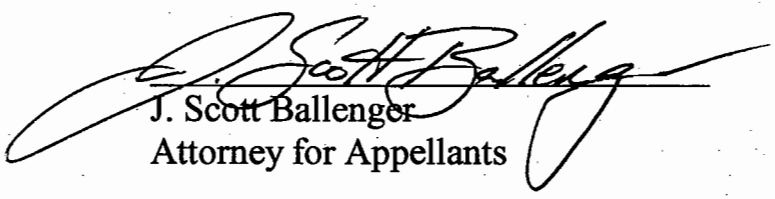
Plaintiff-appellant Abigail Alliance for Better Access to Developmental Drugs is a nonprofit organization based in Fredericksburg, Virginia seeking broader availability of investigational drugs on behalf of its members and terminally ill patients generally. It has no parent company and there is no company with any ownership interest. Plaintiff-Appellant Washington Legal Foundation is a nonprofit public interest law and policy center based in Washington, D.C., with supporters nationwide. It also has no parent company and there is no company with any ownership interest.

Ruling Under Review

The ruling under review is the August 30, 2004 order of the United States District Court for the District of Columbia (Urbina, J.) granting defendants' motion to dismiss for failure to state a claim, and denying defendants' motion to dismiss for lack of subject matter jurisdiction and cross motions for summary judgment by both plaintiffs and defendants. That Order is unpublished, but is provided in the Joint Appendix at JA 49. The accompanying memorandum of law is provided in the Joint Appendix at JA 50-71.

Related Cases

This case has not been previously before this Court and appellants are unaware of any pending related cases.



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OTHER AUTHORITY

GLOSSARY

Abigail Alliance	Abigail Alliance for Better Access to Developmental Drugs
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
IND	Investigational New Drug Application
NDA	New Drug Application
Treatment IND	Use of an Investigational New Drug Treatment

STATEMENT OF JURISDICTION

This Court has jurisdiction pursuant to 28 U.S.C. § 1331. The Order granting defendants' motion to dismiss was entered on August 30, 2004 (JA[1] 49), and notice of appeal was timely filed on September 21, 2004 (No. 04-5350).

STATUTES AND REGULATIONS

Pertinent statutes and regulations have been included in a Statutory Addendum attached to this Brief.

STATEMENT OF THE ISSUES

Whether the liberty protected by the Due Process Clause embraces the right of a terminally ill patient with no remaining approved treatment options to decide, in consultation with his or her own doctor, whether to seek access to investigational medications that the Food and Drug Administration ("FDA") concedes are safe and promising enough for substantial human testing.

STATEMENT OF THE CASE

The FDA reviews the safety and effectiveness of new drugs in a multi-stage clinical trial process that takes an average of about eight years to complete. Drugs intended to treat life-threatening diseases such as cancer or HIV often show significant promise even in the early stages of those trials. For terminally ill patients who have no approved treatment options, access to that drug may be

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[1] Citations to "JA" refer to the Joint Appendix.

literally a matter of life and death. Some patients are able to secure a spot in the trial, but most cannot—because they are too young, too sick, cannot otherwise qualify for the strict protocol of the trial, or because they are unable to travel.

The FDA essentially concedes that forcing such patients to wait for final approval of the drug can be irrational and cruel. If a patient is terminally ill and has no approved treatment options, the FDA will authorize the treatment use of an investigational drug if, in its sole judgment, the available evidence "provide[s] a reasonable basis for concluding that the drug . . . [m]ay be effective for its intended use in its intended patient population" and that it would not pose an "unreasonable and significant additional risk of illness or injury." 21 C.F.R. § 312.34(a), (b). The FDA insists, however, on making that judgment call itself.

Plaintiffs-appellants Abigail Alliance for Better Access to Developmental Drugs ("Abigail Alliance") and the Washington Legal Foundation contend that terminally ill patients with no approved treatment options have a right to decide *for themselves*, in consultation with their own doctor, whether to take an investigational drug that the government concedes is safe and promising enough to be tested in substantial numbers of human subjects.

Prior to any discovery, the district court granted defendants' motion to dismiss for failure to state a claim. *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-cv-1601 (D.D.C. Aug. 30, 2004). A

panel of this Court reversed. 445 F.3d 470 (2006). This Court granted rehearing *en banc* on November 21, 2006.

REGULATORY BACKGROUND

The Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, §§ 1-902, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301 *et seq*, requires a drug manufacturer to file an application and receive FDA approval before introducing any "new drug" into interstate commerce. 21 U.S.C. § 355(a); 21 U.S.C. § 321(p). The original 1938 version only gave the FDA the authority to review the *safety* of new drugs. The FDA was given the additional authority to evaluate the *effectiveness* of new drugs in 1962. For full marketing approval, the statute now requires "substantial evidence" that the drug "will have the effect it purports or is represented to have." *Id.* § 355(d).

Congress authorized an exception for drug distribution "intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." *Id.* § 355(i)(1). The investigation process generally follows three phases. "Phase 1" trials usually involve 20 to 80 subjects, and are intended to "determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a). "Phase 2" normally involves controlled clinical studies of

several hundred subjects, intended to "evaluate the effectiveness of the drug for a particular indication or indications . . . and to determine the common short-term side effects and risks associated with the drug." *Id.* § 312.21(b). "Phase 3" involves expanded controlled and uncontrolled trials, often including several hundred to several thousand subjects, "performed after preliminary evidence suggesting effectiveness of the drug has been obtained." *Id.* § 312.21(c). On average, it takes just under eight years for a drug to pass through all stages and approvals. Christopher P. Adams & Van V. Brantner, *New Drug Development: Estimating entry from human clinical trials* 9 (Jul. 7, 2003), *available at* http://www.ftc.gov/be/workpapers/wp262.pdf.

The FDA has recognized that the statutory exception for "investigational use," 21 U.S.C. § 355(i)(1), permits the treatment use of investigational drugs prior to full approval, even outside the context of a formal clinical trial. The FDA has also recognized that the long delays necessary for full marketing approval frequently mean that a promising new therapy will not become available until it is too late to help patients with serious or life-threatening illnesses. To address that problem, the FDA has given itself authority to make exceptions to the regular NDA approval process. For example, the "Accelerated Approval" program authorizes FDA officials to approve drugs based on evidence of their effects on "surrogate endpoints" (such as tumor shrinkage) or a clinical benefit other than

survival or irreversible morbidity. 21 C.F.R. § 314.510. The "parallel track" protocol provides investigational drugs to patients with life-threatening HIV-related diseases with no satisfactory alternative therapy options as early as after Phase 1 trials. 57 Fed. Reg. 13,250 (Apr. 15, 1992).

The "treatment IND" regulations also allow a physician or IND sponsor to submit a proposal for the use of a drug in the treatment of patients not in clinical trials. 21 C.F.R. §§ 312.34, 312.35. The FDA authorizes treatment IND protocols only if the drug is "intended to treat a serious or immediately life-threatening disease," "there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease," "[t]he drug is under investigation in a controlled clinical trial," and "[t]he sponsor of the controlled clinical trial is actively pursuing marketing approval." *Id.* § 312.34(b)(1)(i)-(iv). But it reserves the right to deny any request if, in its sole judgment, the available scientific evidence does not provide a reasonable basis for concluding that the drug "[m]ay be effective for its intended use in its intended patient population" or that it would not expose patients to "an unreasonable and significant additional risk of illness or injury." *Id.* § 312.34(b)(3). FDA regulations also forbid drug sponsors from "charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug." *Id.* § 312.7(d)(3).

The FDA also reserves the discretion to authorize "emergency" access to unapproved drugs for a particular patient even prior to the submission of an IND based on a request "by telephone or other rapid communication means." *Id.* § 312.36. The regulation provides no guidelines for the exercise of that discretion.

Once a drug has been approved by the FDA as safe and effective for the treatment of any condition, physicians may prescribe (and individual patients may take) that drug "off-label" in any other circumstances where the physician believes that the available scientific evidence justifies its use in another "unapproved" indication. Steven R. Salbu, *Off-Use, Prescription, and marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 188-192 (1999).

The FDA recently issued two proposed rules intended to clarify the existing regulations. *See* Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147 (Dec. 14, 2006); Charging for Investigational Drugs, 71 Fed. Reg. 75,168 (Dec. 14, 2006).

The proposed Expanded Access Rule would retain most of the current regulations for large-scale treatment INDs, while creating two new categories of treatment use for individual patients and intermediate-size patient populations. For all categories, the proposed rule would require the FDA to determine that "the potential patient benefit justifies the potential risks of the treatment use and those

potential risks are not unreasonable in the context of the disease or condition to be treated." 71 Fed. Reg. at 75,151, 75,166. But the FDA concedes that very little evidence regarding safety or effectiveness is needed when a patient is facing an immediately life-threatening disease or condition:

> [T]o support expanded access for an individual patient when the patient has an immediately life-threatening condition that is not responsive to available therapy, ordinarily, completed phase 1 safety testing in humans at doses similar to those to be used in the treatment use, together with preliminary evidence suggesting possible effectiveness, would be sufficient to support such a use.

Id. at 75,151. Indeed, in some cases, "there may be no relevant clinical experience, and the case for the potential benefit may be based on preclinical data or on the mechanism of action." *Id.* The proposal also states that "[f]or a patient with an immediately life-threatening condition, the evidentiary burden could be very low—little if any clinical evidence to suggest a potential benefit or possibly only animal data to support safety of the use." *Id.* at 75,153.

In its proposed Charging Rule, the FDA acknowledges that making investigational drugs available for treatment use is "potentially costly," and hopes that charging will "encourage sponsors to make investigational drugs available to seriously ill patients who lack satisfactory alternative treatment and might benefit from these drugs." 71 Fed. Reg. at 75,170. Nevertheless, the proposed rule would limit charges to recovery of "direct costs" plus any "costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements,

and other administrative costs directly associated with the expanded access." *Id.* at 75,181.[2]

STATEMENT OF FACTS

Because the district court granted defendants' motion to dismiss for failure to state a claim, the allegations of plaintiffs' complaint must be accepted as true.

Patients with life-threatening illnesses currently face immense regulatory barriers to obtaining promising new medications from drug sponsors that are willing to sell or donate those drugs during the years of clinical testing and review. Amend. Compl. ¶ 17 (JA 79). Evidence of the effectiveness of a new drug is often available to physicians specializing in that disease long before the FDA approves the drug. *Id.* at ¶ 16 (JA 79).

Current regulations provide access to experimental drugs only to an extremely small patient population. Spaces in clinical trials are limited and carry stringent selection criteria in terms of patient condition and treatment history. "Treatment IND" programs are currently authorized for only a small fraction of those terminally ill patients in desperate need. Those programs are small, when they exist at all, in part because drug companies may not charge more than cost recovery. *Id.* at ¶ 18, 20 (JA 80).

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[2] The FDA's new proposals essentially restate and clarify existing policy, and do not remotely moot appellants' claims.

Terminally ill patients are often willing to assume risks if their physicians advise them that a treatment may save or prolong their lives and if they have no other viable options. *Id.* at ¶ 19 (JA 80). The effect of FDA policy is to deny patients this choice. To frame the consequences in concrete terms, plaintiffs' complaint includes brief summaries of the case histories of four patients.

Abigail Burroughs

Abigail Burroughs learned at age nineteen that she had head and neck cancer. For the next eighteen months, Abigail fought the cancer with painful chemotherapy and radiation treatments, to no avail. Abigail was told in March of 2001 that she had run out of FDA-approved options. Abigail's cancer cells had very high EGFR (Epidermal Growth Factor Receptors) expression. Her renowned oncologist at Johns Hopkins knew there was a significant chance of saving her life if she could get the new EGFR cancer drug Erbitux. Abigail could not get Erbitux because the ongoing clinical trials were for colon cancer patients only. She died on June 9, 2001, at the age of twenty-one. *Id.* at ¶ 22 (JA 81).

David Baxter

High school student David Baxter was diagnosed with colorectal cancer in the spring of 2001. David was unable to participate in clinical trials because trials are usually open only to patients eighteen and older. He endured various types of

chemotherapy and died in his sleep at home on October 6, 2001, shortly after his seventeenth birthday. *Id.* at ¶ 23 (JA 81-82).

Alita Randazzo

Alita Randazzo, age thirty-five, was diagnosed with colorectal cancer in the spring of 2000. Alita responded well at first to Eloxatin (Oxaliplatin), but had to endure the expense and physical demands of traveling to France to get the drug. (Eloxatin was approved in Europe six years before its approval in the U.S. in May of 2003). She did not qualify for the clinical trial of Eloxatin in the U.S. and was not fortunate enough to get into the drug's limited compassionate use program. After eight months, Eloxatin stopped helping Alita and her doctors believed her last chance was Erbitux. Alita was unable to obtain Erbitux, and died on July 20, 2002. *Id.* at ¶ 24 (JA 82).

Joel Oppenheim

Joel Oppenheim was first diagnosed with multiple myeloma in 1995 but the disease did not become active until 1999. At that time, he was treated with dexamethadrone ("dex"), which had unpleasant side effects and was only minimally effective. *Id.* at ¶ 25 (JA 82-83). As Joel's disease worsened in 2000, his oncologists recommended that he seek to participate in clinical trials of Revamid (now called Revlimid) or PS-341 Velcade. Revamid is a derivative of thalidomide that avoids thalidomide's side effects (which extend well beyond its

notorious effect on pregnant women). Joel's prior treatment with dex put him outside the narrow protocols of the Revamid and Velcade trials, which were oversubscribed in any event. *Id.*

In light of Joel's inability to obtain Revamid or Velcade, his oncologists recommended an autologous bone marrow transplant, which he underwent on April 15, 2001. This is a dangerous and damaging procedure. Joel survived the transplant, but was disabled from working and left with an impaired immune system. *Id.* at ¶ 27 (JA 83).

A year and a half later Joel's cancer worsened again. He again attempted to enter Velcade trials, but was disqualified from some by his prior dex treatment and from others by his transplant (made necessary by his lack of access to Velcade or Revamid). Because one of the criteria of the trials was no drugs within the prior six months, Joel's doctors advised him to stop taking dex or any other treatment. Without medication, Joel's cancer grew much worse. Finally, in June of 2003, Joel was admitted to a trial of Revamid. *Id.* at ¶ 28 (JA 84). Joel died of his long-untreated and undertreated cancer on December 6, 2003.

Appellants have urged the FDA to modify its regulations and internal practices to eliminate regulatory barriers to the treatment use of investigational drugs by terminally ill patients with no approved treatment alternatives. The FDA unequivocally rejected those requests in a lengthy letter dated April 25, 2003. (JA

17-26). On June 11, 2003, appellants filed a Citizen Petition with the FDA pursuant to 21 C.F.R. § 10.30. The FDA acknowledged receipt of the Citizen Petition, but has otherwise not responded. Amend. Compl. ¶ 31 (JA 85).

BRIEF OVERVIEW OF RECENT DRUG DEVELOPMENTS

Appellants respectfully believe that this Court will better appreciate why informed physicians now sometimes conclude that a patient's best hope for survival is an investigational therapy if it has a brief introduction to the kinds of information that sometimes emerge from early clinical trials.

Erbitux in head and neck cancer.

In December of 1994, ImClone began testing targeted a monoclonal antibody C225, later called Erbitux, as a drug to combat cancers that over-expressed EGF receptors. Alex Prud'homme, *The Cell Game* 69, 78 (HarperBusiness 2004). Certain patients in those trials had a near-miraculous response to the drug, which attracted great attention from the press and from oncologists and dying patients. *Id.* at 81-88, 314.

On May 24, 2000 more extensive results of ImClone's studies were presented at the annual meeting of the American Society of Clinical Oncology ("ASCO"). Those results included a remarkable response rate in patients with head and neck cancer for whom chemotherapy alone no longer worked. "All observable signs of the cancer were eliminated in 13 (87 percent) of the 15 patients

who received the drug in combination with radiation therapy. In the remaining two patients, the tumors shrank but did not completely disappear."[3] The results were widely reported around the time that Abigail Burroughs was told by her doctor that she had run out of FDA-approved options.

Imclone chose to focus its subsequent trials on the much more numerous colorectal cancer patients, and the approval process was delayed by a succession of tragic errors and misunderstandings. Erbitux was approved by the FDA for certain colorectal cancers in February of 2004, at which point doctors could also prescribe it for head and neck cancer "off-label."[4] Dr. Mark Thornton, one of the FDA medical reviewers involved in that approval, has stated publicly that there was "'extremely compelling' data on Erbitux for head and neck cancer as early as 2000," and that "'it was hard to argue against providing it to patients.'"[5] Several more studies confirming Erbitux's efficacy in treating head and neck cancer were

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[3] *Monoclonal Antibody Drug IMC-C225 Shows Wide Promise*, AMERICAN CANCER SOCIETY NEWS SERVICE, May 24, 2000, *available at* http://tinyurl.com/y2kqcr.

[4] Kim Coghill, *ImClone's Erbitux Receives Long-Awaited FDA Approval*, BIOWORLD TODAY, February 13, 2004, *available at* 2004 WLNR 267312.

[5] *Drug Reckoning*, WALL STREET JOURNAL, March 6, 2006, *available at* http://online.wsj.com/article_print/SB114161014026390042.html. The Wall Street Journal has been a frequent critic of FDA policy in this area. Several of its editorials are available at http://www.abigail-alliance.org.

published over the next two years.[6] Erbitux was approved by the FDA to treat head and neck cancer on March 1, 2006.[7]

Gleevec in chronic myelogenous leukemia

Chronic myelogenous leukemia ("CML") is a cancer of the bone marrow. Prior to 1998, the only treatments were enfeebling chemotherapy, ineffective interferons, or highly risky bone marrow transplants.

In the 1990s, a team of researchers tested numerous compounds designed to block the cancer-causing protein BCR-ABL. One of these compounds, STI571, was found to inhibit growth of CML cancer cells. Phase I clinical trials of STI571 began in June 1998.[8] Though these initial trials were designed primarily to ensure proper dosage and safety, the demonstrated efficacy of the drug was astounding. *All 31* of the 31 patients receiving daily doses of at least 300 mg of STI571 had

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[6] *See, e.g., Encouraging Data on Cetuximab for Squamous Cell Cancer of the Head and Neck*, ASCO DAILY NEWS, WRAP-UP EDITION, June 5, 2004, *available at* http://tinyurl.com/yfjm3s; *Adding Erbitux (Cetuximab) to Radiation Improves Survival in Patients With Head and Neck Cancer: Presented at ASCO*, DOCTOR'S GUIDE PERSONAL EDITION, June 6, 2004, *available at* http://tinyurl.com/yd2muk; *Erbitux Proven Effective in Locoregional Squamous Cell Carcinoma of the Head and Neck: Presented at AACR-NCI-EORTC*, DOCTOR'S GUIDE PERSONAL EDITION, November 17, 2005, *available at* http://tinyurl.com/yalfx9.

[7] *FDA Approves Erbitux (Cetuximab), First Head & Neck Cancer Treatment in 45 Years*, DOCTOR'S GUIDE PERSONAL EDITION, March 2, 2006, *available at* http://tinyurl.com/yhjajm.

[8] National Cancer Institute, Gleevec: Questions and Answers, *available at* http://www.cancer.gov/cancertopics/factsheet/gleevecqa.

their white blood cell counts return to normal. In nine of the 20 patients treated for at least five months, no evidence of cancer cells could be found. *Id.*

Preliminary results of this Phase I study were announced at a July 1999 meeting, and word spread quickly. The FDA gave full marketing approval to STI571 as Gleevec on May 10, 2001—approximately two years after those first miraculous trial results and, to the FDA's credit, much faster than normal. During those two years, approximately 3,500 Americans died of CML.

Bexxar in non-Hodgkin's lymphoma

Bexxar® (tositumomab) is a radioactive antibody-based therapy for non-Hodgkin's lymphoma ("NHL"), a lethal blood-borne cancer of the immune system. Rabiya S. Tuma, *Bexxar: Birth of a Drug*, 1 CURE (Winter Issue, No. 4, 2003). Of the nine patients treated in the initial Phase I trials, six responded, including four complete remissions.[9] Coulter Pharmaceutical conducted additional trials, and positive preliminary results were reported in May of 1997.[10] All 17 of the advanced-stage patients in the trial showed greater than 50% reduction in tumor

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[9] Ken Garber, *For Bexxar, FDA Meeting Offers Long-Awaited Chance at Approval*, 94 J. NAT'L CANCER INST. 1738 (Dec. 4, 2002), *available at* http://jncicancerspectrum.oxfordjournals.org/cgi/content/full/jnci:94/23/1738.

[10] *Bexxar Effective As First-Line Therapy For Non-Hodgkin's Lymphoma*, DOCTOR'S GUIDE PERSONAL EDITION, May 20, 1997, *available at* http://tinyurl.com/ydza77.

mass, and 16 experienced full or partial remissions. *Id.* Further public studies confirmed that Bexxar would be an effective therapy for NHL.[11]

The FDA denied approval to Bexxar twice, in 1999 and 2002. Coulter Pharmaceutical appealed the FDA's second decision, and in December 2002 an FDA advisory panel voted overwhelmingly to recommend approval.[12] That recommendation was available to physicians treating, and patients dying of, NHL. Bexxar was approved on June 30, 2003.[13] Between 2000 and 2003, approximately 88,419 people died from NHL.[14]

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[11] *See, e.g., Bexxar Effective As Combination Therapy For Non-Hodgkin's Lymphoma*, DOCTOR'S GUIDE PERSONAL EDITION, December 6, 1999, *available at* http://tinyurl.com/yd6fyk; *Durable Responses With Bexxar (Tositumomab) in Transformed Non-Hodgkin's Lymphoma: Presented at ASH*, DOCTOR'S GUIDE PERSONAL EDITION, December 16, 2002, *available at* http://tinyurl.com/ylr3pb.

[12] *See* Transcript of the 73rd Meeting of the Oncology Drugs Advisory Committee to the Food and Drug Administration Center for Drug Evaluation and Research at 203-04, 210-11 (Dec. 17, 2002); *Bexxar (Tositumomab/Iodine I 131 Tositumomab) Receives Strong Support From FDA Advisory Panel*, DOCTOR'S GUIDE PERSONAL EDITION, December 18, 2002, *available at* http://tinyurl.com/ykvrw9.

[13] *See* Cure Article; *FDA Approves Bexxar in Patients With Follicular Non-Hodgkin's Lymphoma*, DOCTOR'S GUIDE PERSONAL EDITION, June 30, 2003, *available at* http://tinyurl.com/ybq43b.

[14] Ries LAG, et al. (eds). *SEER Cancer Statistics Review, 1975-2003*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, *available at* http://seer.cancer.gov/csr/1975_2003//results_single/sect_a_table.03.pdf.

PROCEEDINGS BELOW

Plaintiffs filed this action on July 8, 2003, in the U.S. District Court for the District of Columbia. Prior to discovery, defendants moved to dismiss under Rules 12(b)(1) and 12(b)(6), or in the alternative for summary judgment. Plaintiffs opposed those motions, and moved for summary judgment themselves. The district court denied defendants' 12(b)(1) motion, concluding that plaintiffs' constitutional claim is ripe for review and is not barred by finality or exhaustion principles. JA 58-63. It also denied both motions for summary judgment.

The district court granted defendants' 12(b)(6) motion. It concluded that under this Court's decision in *Dronenburg v. Zech*, 741 F.2d 1388 (D.C. Cir. 1984), it lacked authority to conclude that fundamental rights were implicated unless plaintiffs were asserting a right already "recognized" in a Supreme Court case "directly on point," JA 65-66, or unless the Supreme Court had "'defined a mode of analysis, a methodology, which, honestly applied, reaches the case we must now decide,'" JA 68 (quoting *Dronenburg*, 741 F.2d at 1396). The district court concluded that all of the Supreme Court's prior due process privacy cases can be distinguished from this one, and that therefore "there is no *recognized* fundamental right involved" in this case. *Id.* (emphasis added). It also concluded that "the policy of barring all potentially unsafe and ineffective drugs from interstate commerce until proven by a rigorous testing process, even when it has

the effect of barring access to investigational drugs by terminally ill patients with no other treatment options, is rationally related [to] the legitimate state interest of protecting public health." JA 70-71.

On appeal, a divided panel of this Court reversed. The panel held that the district court felt "unduly constrained" by "advisory cautioning" in *Dronenburg*. 445 F.3d at 475. It concluded that the right sought by appellants satisfies the restrictive *Washington v. Glucksberg*, 521 U.S. 702 (1997), test for fundamental rights because it is deeply rooted in the common law "right of control over one's body," including the traditional rights of self-defense and self-preservation, and because federal regulation of the effectiveness of drugs has been too recent and haphazard "to establish that the government has acquired title to this right by adverse possession." *Id.* at 479-83 & n.24. The panel also held that that right is "implicit in the concept of ordered liberty," based in part on the Supreme Court's reasoning in *Cruzan v. Director, Mo. Dep't of Health*, 497 U.S. 261 (1990). *Id.* at 484-85. It remanded to give the district court a chance to determine whether the FDA policies burdening that right are narrowly tailored to compelling state interests. *Id.* at 486. Judge Griffith dissented.

This Court granted rehearing *en banc* on November 21, 2006, vacating the panel's opinion. That same day, the panel issued an additional opinion concluding (unanimously) that appellants have standing. That opinion has not been vacated.

SUMMARY OF ARGUMENT

In recent decades the science of drug development has accelerated and changed. Companies are no longer just sifting through random compounds in the hope that one will show some drug effect worthy of testing. Instead they are, for example, designing molecules that fit into a well-understood receptor on the surface of a cell like a key into a lock. They are introducing human cancer cells into other mammals in order to trigger an immune response, and then "humanizing" the resulting antibodies so that the human immune system can recognize cancer cells as foreign attackers. Drugs like these have revolutionized the treatment of cancer and other life-threatening illnesses.

Despite the advances, however, some patients still find themselves without any viable approved treatment options—because the approved therapies are known to be ineffective at that stage of the illness, because they have already been tried and failed, or because the patient lacks the strength to survive the side effects. It is now common for such patients to be told by their doctors that their best chance of survival is to get into a clinical trial for a specific new drug under development. That is exactly what Abigail, David, Alita, and Joel were told. Doctors follow the results of ongoing clinical trials with care, and frequently have sound and substantial reasons for concluding that an investigational drug may help a particular patient before (sometimes years before) that drug is approved for general

marketing. By the time Abigail exhausted all her other options and tried to get into the Erbitux trials, for example, it was obvious to many oncologists that Erbitux would be a major advance for head and neck cancer. The evidence for that conclusion in 2001 was perfectly scientific (including statistically valid clinical trial data) and widely available. And the FDA would have been happy to let Abigail take Erbitux, despite any remaining uncertainties, if she had won a spot in the ongoing trials. Thousands of patients find themselves in her position every year: they are terminally ill, they have exhausted all approved treatment options, their doctors believe that a drug currently in Phase 2 or Phase 3 trials might save or extend their lives, but they cannot get into the trial no matter how hard they try.

FDA policy is that patients in that position are allowed to seek access to the drug outside of the trials, and a willing drug company is permitted to provide it, *only* if they come to the FDA, fill out a mountain of regulatory paperwork, and convince FDA officials that the likely benefits outweigh the risks. The panel correctly held that terminally ill patients with no remaining approved treatment alternatives have a fundamental right to make the basic risk / benefit decision for themselves, in consultation with their treating physician. All they want is the right to fight for their own lives by taking a drug that their doctor has concluded is justified by the available scientific evidence, and that the FDA itself is happy to let them take if they are lucky enough to get a spot in the trials. The FDA concedes

that, given the available evidence, a trial in several hundred or several thousand patients is ethical, and that a patient could reasonably decide to participate and give informed consent.

Substantive due process cases are often controversial, but this one should not be. The Supreme Court has already acknowledged that the Due Process Clause guarantees terminally ill patients the right to choose for themselves whether to refuse potentially life-sustaining treatment (including even nutrition and hydration) and die. Surely a patient's interests in autonomy and privacy are no less fundamental if she instead chooses to fight for her life, whatever the odds, by taking an incompletely studied investigational drug. Either way, these decisions express not just a medical or scientific judgment but also the patient's life circumstances and basic philosophical commitments. They are at least as central to an individual's right to define the course and meaning of his or her own life as the decisions about marriage, procreation, parenting, and sexual behavior that the Supreme Court has previously held implicate fundamental rights.

The right recognized by the panel is also firmly grounded in historical tradition, in at least two distinct ways. First, it is essentially required by the traditional common law right of self-defense and related doctrines such as necessity and interference with rescue. Persons facing a real threat to their lives have always had a strong privilege to defend themselves, including by means that

would otherwise violate the law. They may even use lethal force to protect themselves when the target of that force is morally innocent, and even if that attempt at self-defense is uncertain or unlikely to succeed. That self-defense right is at the very heart of traditional Anglo-American liberty. The Framers called it the "first law of nature." Since a person has the right to risk the lives of others in an attempt to save his own, surely he also has the right to take some risks *with his own life* in a good faith effort to save it. Indeed patients take such risks all the time, with surgery and with "approved" but dangerously toxic drugs such as chemotherapy.

Nothing about the medical context renders self-defense principles inapplicable. Completely apart from the controversial right to abortion in the service of reproductive autonomy recognized in *Roe v. Wade*, 410 U.S. 113 (1973), there has always been a separate right to abortion throughout pregnancy when necessary to protect the mother's life. That right was recognized by all 50 states pre-*Roe*, and rests squarely on traditional self-defense principles. Even then-Justice Rehnquist, in dissent in *Roe* itself, recognized that denying that right to self-defense abortion would be unconstitutional. 410 U.S. at 173. This case simply calls for an application of traditional self-defense principles in a medical context without all of the countervailing historical and moral considerations that make the abortion cases difficult and controversial.

Second, the common law consistently left judgments about the efficacy of medical treatments in the hands of individual doctors and their patients. Governmental review of the effectiveness of drugs did not exist in this country at all until 1962, and even today full FDA approval requires only that clinical trials prove effectiveness *for something*. Once that hurdle is cleared, doctors can and do prescribe drugs "off-label" for other conditions where the doctor's belief in its possible efficacy may be based on little more than an informed hunch.

A great many cancer treatments today are "off-label" uses, such as the widespread use of Thalidomide to treat cancer when, until very recently, it was approved only for leprosy. And even unapproved drugs have always still been available, in theory at least, to terminally ill patients with no other options. There is not, and has never been, any real or consistent federal policy of forcing terminally ill patients to wait for the outcome of elaborate multi-stage trials.

The FDA has adopted a wide array of accelerated approval and exemption procedures, and now even concedes that it is "ordinarily" appropriate for terminally ill patients with no other options to have access to investigational drugs after Phase 1. 71 Fed. Reg. at 75,151. The remaining disagreement in this case is just that the FDA insists on retaining the *ad hoc* discretion to weigh the likely risks and benefits for each patient. The historical pedigree for that arbitrary and unaccountable exercise of state power is short and undistinguished.

The FDA and its amici will no doubt assert a variety of public policy objections to expanding access to investigational drugs. The panel wisely recognized that those arguments relate not to the patient's liberty rights, but instead to whether FDA interference with that liberty might be justified by various compelling interests—such as the need to protect patients from harmful drugs or price-gouging, or the need to maintain incentives for participation in clinical trials. Those issues should be considered by the district court on remand after factual development. If the autonomy of terminally ill patients in these matters has to be overridden for compelling societal reasons, then so be it. But the basic dignity and humanity of these patients demands more justification for overriding their own choices than the tissue paper barrier of rational basis review. If this Court chose to reach the narrow tailoring issues on the present record, it should hold that the FDA has not remotely justified its present policies.

ARGUMENT

I. TERMINALLY ILL INDIVIDUALS WITH NO APPROVED TREATMENT OPTIONS HAVE A FUNDAMENTAL LIBERTY INTEREST IN DECIDING, WITH THEIR DOCTORS, WHETHER TO PURSUE INVESTIGATIONAL TREATMENTS

The Supreme Court has explained that the Due Process Clause protects those rights that are "'implicit in the concept of ordered liberty,'" and "'deeply rooted in this Nation's history and tradition.'" *Glucksberg*, 521 U.S. at 721 (citations omitted). The right of terminally ill patients with no other treatment options to

take investigational drugs that the government has approved for substantial human trials satisfies both standards.

A. Allowing Individual Choice Concerning Potentially Life-Saving Drugs Is Implicit In The Concept Of Ordered Liberty

The Supreme Court has repeatedly held that the Constitution protects a basic right of individual autonomy and privacy in making certain fundamentally personal decisions. Whether that right is located in the "liberty" protected by the Due Process Clause or is implied by the more specific provisions of the Bill of Rights, *see Griswold v. Connecticut*, 381 U.S. 479, 484 (1965), it embraces the freedom for individuals to decide for themselves whom to marry, *Loving v. Virginia,* 388 U.S. 1 (1967); *Zablocki v. Redhail*, 434 U.S. 374 (1978), how their children will be raised and in what language they will be educated, *Meyer v. Nebraska*, 262 U.S. 390 (1923); *Wisconsin v. Yoder*, 406 U.S. 205 (1972), whether to possess and view pornography in the home, *Stanley v. Georgia*, 394 U.S. 557 (1969), and whether to engage in private sexual relationships contrary to criminal statutes, *Lawrence v. Texas*, 539 U.S. 558 (2003). *See generally Meyer*, 262 U.S. at 399 ("the right of the individual to contract, to engage in any of the common occupations of life, to acquire useful knowledge, to marry, establish a home and bring up children, to worship God according to the dictates of his own conscience, and generally to enjoy those privileges long recognized at common law as essential to the orderly pursuit of happiness by free men."). The Court has also held that it guarantees the

right to make certain inherently personal medical decisions, including a right of access to contraceptive drugs that the State has banned, *Griswold*, 381 U.S. 479 (1965); *Eisenstadt v. Baird*, 405 U.S. 438 (1972), and a right to refuse life-sustaining medical treatment (including even nutrition and hydration) and thereby choose to die, notwithstanding the State's strong interest in life and our society's longstanding prohibition against suicide. *Cruzan*, 497 U.S. at 281.

Decisions concerning the treatment of life-threatening diseases are among the most profoundly private and significant in life. Unlike even the private choices involved in marriage, parenting, and sexual behavior,

> [medical decisions] are, to an extraordinary degree, intrinsically personal. It is the individual making the decision, and no one else, who lives with the pain and disease. It is the individual making the decision, and no one else, who must undergo or forego the treatment. And it is the individual making the decision, and no one else, who, if he or she survives, must live with the results of that decision.

Andrews v. Ballard, 498 F. Supp. 1038, 1047 (S.D. Tex. 1980). The personal nature of medical decisions is amplified for terminally ill patients with no approved treatment options. Such individuals confront the terrible reality that, absent some experimental form of treatment, they are virtually certain to die in a few months. It demeans the dignity of these patients and the magnitude of what they are facing to suggest that deciding whether to marry, use contraception, engage in homosexual sex, or teach their children German is more fundamentally private, personal, or central to their autonomy as a human being than deciding for

themselves whether the risk is too great, or the hope too little, to justify trying a promising but unproven experimental drug when the alternative is passive resignation to imminent death.

Any doubt on that score is dispelled by *Cruzan*, which recognized the "common-law tradition of medical self-determination" as a "well-established rule of general law." 497 U.S. at 306. The Supreme Court acknowledged in *Cruzan* that "[t]he principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions," and even assumed that the Due Process Clause "would grant a competent person a constitutionally protected right to refuse lifesaving hydration and nutrition," and thereby choose death, even if they were not terminally ill. 497 U.S. at 278-79. If a patient has a fundamental right to medical self-determination that gives them the right to starve themselves to death, then surely they have a right to choose to fight for their lives even if that means taking a drug that has not yet met the FDA's full approval standards. As one commentator put it:

> It is ironic that the courts protect the right to refuse medical treatment when in some instances such treatment would save life but refuse to protect the right of a terminally ill patient to accept treatment of unknown efficacy as a last resort to preserve life. The decision to live should be considered more important than the decision to die; for courts to protect the latter but not the former is more than inconsistent, it is absurd.

V. Anthony Unan, *The Right to Choose an Unproven Method of Treatment*, 13 Loy. L.A. L. Rev. 227, 235 (1979); *see also* Jon Scott Batterman, Note, *Brother Can You Spare A Drug: Should The Experimental Drug Distribution Standards Be Modified In Response To The Needs Of Persons With AIDS?*, 19 Hofstra L. Rev. 191, 217 (1990) (arguing that it would be "illogical to recognize the fundamental right of a patient to refuse necessary medical treatment . . . while refusing to recognize the fundamental right of a terminal patient with no approved treatment alternatives to elect to use an unapproved experimental drug"). The patient's autonomy interests are the same no matter which decision they make, and if they choose to seek experimental treatment they are also invoking their traditional right to self-defense, discussed *infra*, and their fundamental right to *life*, which is protected along with liberty in the plain text of the Due Process Clause. The Supreme Court recognized in *Cruzan* that "[t]he choice between life and death is a deeply personal decision of obvious and overwhelming finality," and that "[i]t cannot be disputed that the Due Process Clause protects an interest in life as well as an interest in refusing life-sustaining medical treatment." 497 U.S. at 281.

The district court attempted to distinguish *Cruzan* by suggesting that it involved "freedom against government imposition," whereas plaintiffs here are seeking "an affirmative right of access to medical treatment," JA 68, or a "right to *receive* medical treatment," JA 66. Plaintiffs are not looking for a handout, or for

an "affirmative right" to government assistance of any kind. All they ask is that the government get out of their way, so that they can use their own private resources to fight for their own lives at the inherently uncertain frontiers of modern science. To be precise they ask only that a voluntary transaction between consenting adults—a purchase or donation of investigational drugs from a willing drug company—be decriminalized in certain narrow circumstances. That is exactly what the plaintiffs sought and obtained in *Griswold* and *Eisenstadt*: a "right of access" to a medical product that was prohibited by law.

It is also important to recognize that the autonomy interests at stake for these patients cannot be reduced to a simple empirical disagreement between their doctors and the FDA about exactly how likely it is that a particular investigational drug will help them. There can be room for reasonable disagreement on such issues. But these decisions often express the patient's life circumstances and philosophical commitments as well as his or her cold assessment of the statistical response rates. Are the last days of a person's life better spent in perhaps painful struggle against nearly impossible odds, but with some hope and the conviction that he or she is doing everything possible? Or is it instead better or more noble to accept one's fate and spend the final days saying goodbye and hoping passively for a spontaneous remission?

Certainly plaintiffs do not know the right answer for every patient. Neither, with great respect, does the FDA. Its current regulations deny terminally ill patients the autonomy to make for themselves, in consultation with their own physician, the last profound, self-defining choice of their lives. That transcends the merits of any disagreement about how to interpret the (often ambiguous) early evidence from a particular clinical trial. A patient's right to make that decision would have great value even if experimental treatments were never successful—which is certainly not true. (The FDA itself has "found that in many situations, individuals or specific patient populations have benefited from increased access to a drug that has not yet been approved for marketing." 71 Fed. Reg. at 75,160.) Acknowledging the fundamental significance of patient choice in these matters is a basic demand of human dignity.

Even the FDA recognizes that forcing terminally ill patients with no other options to wait for elaborate proof of "effectiveness" from multi-stage clinical trials would be unreasonable and cruel. It has reserved to itself enormous discretion to approve treatment use of investigational drugs at any point in the trial process after basic Phase 1 safety has been demonstrated. Such decisions inevitably involve an exercise of sound human judgment in the face of enormous uncertainty. The FDA's true position thus is not that scientifically unproven medications should never be made available—but rather that these incredibly

difficult and uncertain judgments should be made by government regulators rather than by patients and their own doctors. That does not guarantee that the decisions made will be better or any more "scientific."[15] But it does guarantee that patients will be denied the fundamental autonomy to direct the course of their own lives.

B. Allowing Terminally Ill Individuals To Select Investigational Drugs With Their Physicians Is Deeply Rooted In Historical Tradition

The liberty sought by appellants is deeply rooted in the historical traditions of our country and of the common law. FDA policy in this area is inconsistent with the way that our legal tradition treats persons in all other life-threatening situations. And the common law and historical American practices have traditionally trusted individual doctors and their patients with almost complete autonomy to evaluate the efficacy of medical treatments. The supposed federal

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[15] Smart doctors outside the FDA can review the data and make good decisions about how to treat a particular patient, and there is frequently good scientific evidence for effectiveness well before formal approval. Over the past few years Abigail Alliance has fought for earlier access to several drugs for cancer and other life-threatening illnesses, and every one has subsequently been approved by the FDA. (The drugs are Gleevec, Eloxatin, Erbitux, Revlimid, Velcade, Tysabri, Nexavar, Avastin, Tarceva, Sutent, and Bexxar.) The patient's condition and medical history also matter, and FDA officials cannot possibly "play the role of physician to the half million cancer patients who will die this year." Michael Horwin, *"War On Cancer:" Why Does The FDA Deny Access To Alternative Cancer Treatments?*, 13 ALB. L.J. SCI. & TECH. 681, 710 (Summer/Fall 2003). And the separate "parallel track" that the FDA adopted for HIV therapies demonstrates that its treatment of terminal illnesses will always have a political component.

"policy" that the FDA invokes here is no more than a few decades old, and only inconsistently and arbitrarily applied even during that period.

1. Self-Defense, Necessity, and Interference With Rescue

The traditions of our country and the common law have always recognized that persons in mortal peril have the right to try to save their own lives, even if the chosen means would otherwise be illegal or involve enormous risks. That commitment is reflected in several traditional doctrines, including the defenses of self-defense and necessity, and the tort of interference with rescue. The persons who framed and ratified the Constitution and the 14th Amendment understood those privileges as a core aspect of traditional Anglo-American liberty, and would have viewed the governmental intrusion at issue here in those terms.

As Samuel Adams explained in 1772, "[a]mong the natural rights of the Colonists are these: First, a right to life; Secondly, to liberty; Thirdly, to property; together with the right to support and defend them in the best manner they can. These are evident branches of, rather than deductions from, the duty of self-preservation, commonly called the first law of nature." Samuel Adams, *The Rights of the Colonists, The Report of the Committee of Correspondence to the Boston Town Meeting*, Nov. 20, 1772, Old South Leaflets no. 173, *available at* http://history.hanover.edu/texts/adamss.html. The right to take action thought necessary to self-preservation was commonly understood during the colonial

period as not merely one of the "self-evident" natural rights of man, but as the foremost and most obvious: the "first law of nature." *See* 1 ST. GEORGE TUCKER, BLACKSTONE'S COMMENTARIES app. 300 (1803) (describing "[t]he right of self defense" as "the first law of nature."); JOHN LOCKE, TWO TREATISES ON GOVERNMENT, § 207 ("A man with a sword in his hand demands my purse in the high-way, when perhaps I have not twelve pence in my pocket: this man I may lawfully kill" because "the law could not restore life to my dead carcass."). This belief is as old as Western philosophy. *See, e.g.,* Cicero, *In Defense of Titus Annius Milo*, SELECTED POLITICAL SPEECHES 222 (M. Grant trans., 1969) ("if our lives are endangered by plots or violence or armed robbers or enemies, any and every method of protecting ourselves is morally right.").

Of course state law on self-defense has always differed on some details. But federal and state courts have recognized throughout our country's history that at least the core of the traditional right to defend one's own life is constitutionally protected. "Rooted in the Anglo-American tradition is the belief that a killing in self-defense is not a crime." *Thomas v. Leeke*, 725 F.2d 246, 250 n.2 (4th Cir. 1984) (abrogated on other grounds). The Sixth Circuit has held that "the right of a defendant in a criminal trial to assert self-defense" is one of the "few customs and principles 'so rooted in the traditions and conscience of our people as to be ranked as fundamental,'" and that "failure to instruct a jury on self-defense when the

instruction has been requested and there is sufficient evidence to support such a charge violates a criminal defendant's rights under the due process clause." *Taylor v. Withrow*, 288 F.3d 846, 851 (6th Cir. 2002). A plurality opinion of the Supreme Court, authored by Justice Scalia, also recognized that "the historical record may support" the proposition "that the right to have a jury consider self-defense evidence . . . is fundamental." *Montana v. Egelhoff*, 518 U.S. 37, 56 (1996).

Several state courts have reached the same conclusion. The West Virginia Supreme Court has held, for example, "that there [is] a constitutional right to self-defense guaranteed to all persons under both the due process clause of the fourteenth amendment to the *United States Constitution* and article III, section 1 of the *West Virginia Constitution.*" *State ex rel. City of Princeton v. Buckner*, 377 S.E.2d 139, 142 (W.V. 1988) (citing *State v. Workman,* 14 S.E. 9, 10-11 (1891)); *see also State ex rel. Standard Fire Ins. Co. v. Gantt*, 203 S.W. 964, 972 (Mo. 1918) (noting that the United States and Missouri Constitutions protect the rights to life, liberty, and property, and that the right to self-defense is encompassed within those rights.); *People v. Pignatoro*, 136 N.Y.S. 155, 160 (N.Y. City Magistrates Ct. 1911) ("The right of self-defense is an inherent right of man, older than states or Constitutions."); *State v. Cromwell*, 9 N.W.2d 914 (N.D. 1943) (noting that section I of the North Dakota constitution "embodies the essence of the statement of the 'self-evident truths' set forth in the Declaration of Independence,"

and that "[w]ithin the meaning of the term 'liberty' is also included the right . . . of self-defense against unlawful violence . . . .") (citations and quotation marks omitted); *Sinclair v. Mississippi*, 132 So. 581, 586 (Miss. 1931) (J. Etheridge concurring) ("Could the legislature, consistent with due process of law, abolish the right of self-defense? Manifestly it could not, and no person will disagree with this statement."); *cf. Kasler v. Lockyer*, 2 P.3d 581, 602 (Cal. 2000) (Brown, J., concurring) ("But surely, the right to preserve one's life is at least as fundamental as the right to preserve one's privacy."). Forty-four out of fifty state constitutions explicitly protect a right to self-defense in some form.[16]

The traditional right of self-defense allows a person whose life or liberty is threatened to resist with any force necessary, up to and including killing the attacker. Threatened persons may use any means they choose, not simply the best or least harmful means, to protect themselves. *See Gross v. Commonwealth*, 186 S.W.2d 190, 193 (Ky. 1945) (approving instruction that a "defendant was justified

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[16] *See* Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs* 13 (forthcoming Harvard Law Review, April 2007), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=941868. Professor Volokh concludes that the history discussed above supports appellants' position in this case. He also draws a further conclusion—that the right to self-defense embraces a right to buy and sell organs—that is ahistorical and that appellants do not endorse. Organ sale bans are justified by concerns about exploitation, the commoditization of the human body, and treating human beings as means rather than as ends in themselves, that have deep roots in the law. In this case it is appellees who insist on treating the bodies and lives of terminally ill patients as means (to further clinical trial protocols) rather than as ends.

in using any means at hand to protect himself, his body and life against harm."); *State v. Jordan*, 5 S.E.2d 156, 157 (N.C. 1939) ("any means at his command"); *Hall v. State*, 60 S.W. 769, 770 (Tex. Crim App. 1901) ("any means within his power"). That right does not depend on the attacker being morally culpable; a person is entitled to defend themselves against animals, children, and the insane,[17] and is even blameless if he inadvertently kills an innocent bystander, *see Brown v. State*, 94 So. 874 (Fla. 1922). It also privileges even self-defense that government officials might consider imprudent or excessively dangerous to the defender himself. Indeed, safety guidelines counsel persons being mugged to turn over their possessions and flee,[18] and the conventional wisdom is that attempted self-defense by firearm is often counterproductive. Fighting back may dramatically increase the risk of harm, but nonetheless remains well within the victim's rights.

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[17] *See, e.g.*, *id.* at 8; George Christie, *The Defense of Necessity Considered from the Legal and Moral Points of View*, 48 DUKE L.J. 975, 1015 n.206 (1999) (discussing "innocent threat[s]," and stating that "as any law student knows, the right to act in self-defense does not require that the person against whom one is acting is about to violate your rights."); MODEL PENAL CODE §§ 3.04, 3.11(1); 2 AM. LAW. INST., MODEL PENAL CODE AND COMMENTARIES § 3.11, at 159 (1985); Paul H. Robinson, CRIMINAL LAW DEFENSES § 131(b), n.13 (1984 & Supp. 2005).

[18] *See, e.g.*, http://educationusa.state.gov/life/everyday/safety.htm ("Do not fight back as this might provoke your attacker to cause you harm.")

The related traditional doctrine of necessity permits a person to encroach upon the rights or property of others to prevent serious harm to himself. Necessity applies with special force when the object of protection is not property, but life.[19]

Efforts to save the lives of others are also traditionally protected. The common law tort of interference with rescue imposes liability upon any person who intentionally prevents a third person from giving another aid necessary to prevent physical harm. *See* Restatement (Second) of Torts § 326. "[P]reventing the third person from using a chattel" in order to effect a rescue is also tortious. *Id.* cmt. a. These fact patterns rarely arise, but the doctrine is alive and well. *See, e.g.*, *Soldano v. O'Daniels*, 141 Cal. App. 3d 443 (1983) (holding barkeep liable for refusal to permit patron's use of phone to aid another). Government interference with private rescue attempts have been held to violate due process. *See Ross v. United States*, 910 F.2d 1422, 1433-34 (7th Cir. 1990) (holding officer liable for preventing private, competent dive rescue until arrival of on-duty personnel); *see also Andrews v. Wilkins*, 934 F.2d 1267, 1270-71 (D.C. Cir. 1991) (recognizing that *Ross* identified state interference with private rescue efforts as a constitutional tort, but distinguishing *Ross* on the facts); *see also id.* at 1275 (Mikva, J., dissenting in part) ("[a]rbitrarily preventing a private rescue effort that had the greatest likelihood of success constituted a breach of [constitutional] duty").

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[19] *See* Christie, supra note 17, at 986-88 (discussing cases); Volokh, *supra* note 16, at 987-94.

All of these principles support the conclusion that a patient who is threatened with imminent death, and who has no approved treatment options, has a fundamental right to attempt to save his own life by attempting an investigational therapy recommended by his doctor. Our legal tradition has always recognized that life-threatening circumstances are special, and that the autonomy of persons in such situations requires that we tolerate reasonable attempts at self-preservation—even if the means chosen would otherwise be unlawful, and even if those means greatly increase the risk of death for both the attacker *and the attacked*. (In any event it makes no sense to suggest that a person has the right to try to save their own lives by killing someone else, but no right to risk their own lives in the same attempt). There is no meaningful moral or legal difference between a person facing attack by an animal, and a person being attacked by mutated cancer cells. And this situation does not raise any of the borderline issues in self-defense law that might be outside the constitutionally protected core. *E.g.,* Volokh, *supra* n.16 at 9 n.33. This case also presents a classic interference with rescue situation. Physicians are trained to rescue and are entrusted by the FDA itself to make judgments about appropriate medical treatment, including judgments about the possible efficacy of unproven medications (such as in "off-label" situations or when advising a patient to enroll in a trial).

The application of traditional self-defense and necessity principles in the medical context can be seen most clearly by looking at the one medical procedure sometimes banned at common law: abortion. In *Roe*, the Supreme Court recognized a controversial new right to abortion prior to viability as a requirement of constitutional privacy. But it has also recognized another, entirely separate right to abortion: a woman's right to abort a fetus *at any stage of a pregnancy* if doing so is necessary to preserve her life or health. That right is grounded in traditional self-defense principles rather than privacy, and is relatively uncontroversial.

In *Steinberg v. Brown*, 321 F. Supp. 741 (N.D. Ohio 1970), decided three years before *Roe*, the court held that Ohio's criminal abortion statute, which barred abortion unless "such miscarriage is necessary to preserve her [the mother's] life," was constitutional because the state's compelling interest in protecting the fetus could only be trumped if the abortion was necessary to save the mother's life. *Steinberg*, 321 F. Supp. at 746. The court grounded the "life of the mother" exception squarely in the historical tradition of self-defense:

> Obviously, of course, there are limits to the protection which the state can and must extend to human life, but these are clear and well-marked in the law, and have been for centuries, essentially on the basis that "self-preservation is the first law of nature." Thus throughout the development of our law, self-defense has always been recognized as a justification for homicide. Hence the provision in the statute here in question that abortion is noncriminal when it is necessary, or declared by two physician to be necessary, to preserve the life of the mother. One human life may legally be terminated when doing so is necessary to preserve or protect another or

others.

Id. at 747; *see also McRae v. Califano*, 491 F. Supp. 630, 695 (E.D.N.Y. 1980) (summarizing testimony that "[t]he exception allowing abortion in the case in which the mother's life is threatened was in the nature of a justifiable homicide, the equivalent to killing in self-defense."); *id.* at 760 (noting that during debates on the Hyde Amendment Senator Jesse Helms argued that the amendment should not prohibit funding for life-saving abortions because "the doctrine of self-defense is applicable here").

In *Roe*, the Supreme Court recognized a new right to abortion, based in privacy and reproductive autonomy, during the first two trimesters of pregnancy. It held that states could ban abortion after the second trimester "except where it is necessary, in appropriate medical judgment, for the preservation of the life or health of the mother." *Roe*, 410 U.S. at 165; *see also Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833, 879 (1992) (reaffirming exception). The historical record cited by the Court in *Roe* demonstrates that this "life or health of the mother" exception was firmly entrenched in historical tradition. *Roe*, 410 U.S. at 130-141. The Court noted that, in addition to Texas, every state that criminalized abortion nevertheless provided an exception for abortions performed to save the life of the mother. *Id.* at 139-40, *citing* Eugene Quay, *Justifiable Abortion – Medical and Legal Foundations*, 49 Geo. L.J. 395, 435-38 (1961). Even Justice

Rehnquist in dissent in *Roe* expressed his belief that the Constitution would protect a woman's right to an abortion to save her life, stating that "[i]f the Texas statue were to prohibit an abortion even where the mother's life is in jeopardy, I have little doubt that such a statute would lack a rational relation to a valid state objective under the test stated in *Williamson supra.*" *Roe*, 410 U.S. at 173 (Rehnquist, J., dissenting), *citing Williamson v. Lee Optical Co.*, 348 U.S. 483, 491 (1955).

The Supreme Court reaffirmed the constitutional right to abortion necessary to protect the mother's life or health, and the "appropriate medical judgment" standard, *unanimously* just last Term. *Ayotte v. Planned Parenthood*, 126 S. Ct. 961, 967 (2006). New Hampshire actually argued in *Ayotte* that its abortion statute did not need an explicit "health of the mother" exception because it was supplied by the State's general "competing harms" defense—which is basically a codification of common law self-defense and necessity principles. *See Planned Parenthood v. Heed*, 390 F.3d 53, 61 (1st Cir. 2004). The First Circuit and Supreme Court did not think the competing harms statute clear enough, but the argument illustrates the self-defense roots of these exceptions.

Just like ordinary self-defense, the right of medical self-defense exists even when the patient's efforts to save her own life are not certain to succeed, and even if the means chosen would otherwise violate the law. These issues are illustrated

most dramatically by *Stenberg v. Carhart,* 530 U.S. 914 (2000), in which the State of Nebraska, backed by various medical groups, contended that partial birth abortion should be banned even when necessary to protect the *health* of the mother (threats to her life were excepted) because the procedure "may create special risks" to the mother not posed by other procedures, and because "there are no medical studies 'establishing the safety of the partial-birth abortion/D & X procedure.'" The Supreme Court acknowledged the "division of opinion among some medical experts . . . [and] absence of controlled medical studies that would help answer these medical questions." *Id.* at 933, 936-37. It nonetheless held that since "[d]octors often differ in their estimation of comparative health risks and appropriate treatment," the state must "tolerate responsible differences of medical opinion—differences of a sort that the American Medical Association and American College of Obstetricians and Gynecologists' statements together indicate are present here." *Id.* at 937. In other words, no abortion statute can interfere with the responsible medical judgment of a woman and her doctor—even if the state and other doctors believe the procedure unsafe and no scientific evidence resolves that dispute.

The Supreme Court may well reconsider or limit *Stenberg* this Term. But the aspects of *Stenberg* that are controversial are not relevant here. *Stenberg* involved a procedure that many believe to be morally indistinguishable from

infanticide, and the cases before the Court this Term involve explicit findings by Congress that the procedure is *never* medically indicated—which would be akin, in this case, to an explicit determination by the FDA that a drug is unsafe or ineffective and should not be tested further. Appellants' claim is infinitely more cautious. The medical therapies they seek do not implicate any of the powerful moral considerations invoked by the *Stenberg* dissenters, and the FDA has not remotely made a finding that they are unsafe (or even ineffective). The FDA is simply agnostic because safety and efficacy have not yet been shown. Even if the Supreme Court holds that explicit legislative findings regarding the safety of a particular procedure can trump the medical judgment of a treating physician, there are no such findings here.[20] And finally, even the Nebraska statute challenged in *Stenberg* permitted partial birth abortion if necessary to save the life of the mother. Appellants face grave threats to their lives, not merely their health.

It cannot possibly be the law that terminally ill patients, in consultation with their doctors, have a fundamental right to attempt to save their own lives with an

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[20] Justice Kennedy's dissent in *Stenberg* insists that the State has power to resolve disputes about medical issues, and framed the question as "whether there was substantial and objective medical evidence to demonstrate that the State had considerable support for its conclusion that the ban created a substantial risk to no woman's health." 530 U.S. at 969. That reasoning is perfectly consistent with appellants' position here. The FDA certainly *has not* reached any conclusion, akin to Nebraska's in *Stenberg*, that patients in appellants' position all have other medically safe alternatives and therefore could not be harmed by being denied access to investigational drugs. They do not have such alternatives.

unproven course of medical treatment that the government fears may be unsafe or ineffective *only* if that treatment happens to be abortion. That would be absurd, but the absurdity is easily resolved by recognizing that the fundamental right to abortion when necessary to protect the life of the mother has nothing to do with the controversial reproductive autonomy right recognized in *Roe*. It is, instead, simply the expression in one particular context of a traditional right to self-defense shared by all persons whose lives are seriously threatened, medically or otherwise.

2. The History of Drug Regulation

The panel's opinion contains an overview of the history of drug regulation at common law and in this country. The bottom line is that the government never interfered with the judgment of individual doctors about the medical efficacy of particular drugs until 1962. At common law and in colonial America, drug regulation (by government or, more commonly, by professional guilds of doctors or pharmacists) was directed at identifying adulterated or mislabeled drugs so that patients and doctors could be sure about what they had. Edward Kremers & George Urdang, *History of Pharmacy: A Guide and a Survey* 94 (J.B. Lippincott Co. 1949). The 1736 Virginia "act for regulation of the fees and accounts of the practicers in physic" cited by the panel dissent merely required those selling drugs to list the content, amount, and price of the medications they were selling. *Id.* at 142. Neither that Act nor any of the later regulations cited by the dissent (many of

which just restricted public sale of poisons in states with large slave populations) restricted the *medical* use of particular compounds on safety or efficacy grounds. Throughout the period when the Bill of Rights and the Fourteenth Amendment were ratified, privately manufactured "nostrums" and "proprietaries" were freely available and monitored solely by the free market and private organizations like the American Medical Association. *See* Harry F. Dowling, *The American Medical Association's Policy on Drugs in Recent Decades, in Safeguarding the Public: Historical Aspects of Medicinal Drug Control* 123 (John B. Blake ed., 1970).

Public concern about contaminated food and drugs eventually led to the 1906 Food and Drugs Act. Federal Food and Drugs Act, Pub. L. No. 59-384, §§ 1-13, 34 Stat. 768 (1906) (repealed 1938). But that Act required no pre-market review of drugs for safety or efficacy at all, merely mandating that their contents be correctly and fully described. In *United States v. Johnson*, 221 U.S. 488 (1911), the Supreme Court held that the 1906 Act did not prohibit a drug manufacturer from marketing an ineffective cancer remedy with false therapeutic claims, so long as it was not adulterated. In 1938 Congress enacted the FDCA, which for the first time authorized the FDA to review the safety of new drugs. But it was not until 1962 that Congress first authorized the FDA to review whether new drugs were *effective*. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

Even after that point, the FDA has always permitted doctors to exercise their own judgment about "off-label" uses, where, by definition, the clinical proof of effectiveness is not yet sufficient to satisfy the FDA. In one recent survey, 44 of 46 cancer drugs studied were prescribed off-label.[21] The FDA also has always recognized that exceptions need to be made for terminally ill patients with no remaining options. Hence it has adopted a wide array of accelerated approval and emergency use exemptions giving its own staff the authority to permit treatment use of investigational drugs prior to formal clinical proof of effectiveness.

Denying a terminally ill patient with no approved treatment options the right to purchase a promising experimental drug, simply because that drug has not yet been proven effective in the estimation of government regulators, goes against the grain of historical American practice. The numerous exceptions in the FDA's current and proposed regulations make it clear that the district court was simply wrong to say that Congress or the FDA have a consistent "policy of barring all potentially unsafe and ineffective drugs from interstate commerce until proven by a rigorous testing process." JA 70. There is no such policy, even today. At most we

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[21] *See* Misuse of Prescription Drugs: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations, House Comm. on Gov't Reform and Oversight, 104th Cong. 2d Sess. (Sept. 12, 1996) (statement of Sarah F. Jagger, Director of Health Services Quality and Public Health Issues, General Accounting Office).

have seen a few decades of half-hearted and inconsistent interference by the FDA with the treatment decisions of terminally ill patients and their doctors.

The panel dissent correctly noted that a history of non-regulation in a particular area does not necessarily establish a historical understanding that regulation would be inconsistent with basic liberties, and argues that "[t]he history of drug regulation in this country does not evidence a tradition of protecting a right of access to drugs; instead, it evidences government responding to new risks as they are presented." 445 F.3d at 495 (Griffith, J., dissenting). With respect, the dissent demands the impossible. Appellants cannot cite specific common law decisions affirmatively protecting the right they seek, because at common law no government ever attempted to overreach in this way. The same was true in many of the Supreme Court's cases. A history of non-regulation is not conclusive proof that regulation would have been considered inconsistent with traditional rights, but it is at least suggestive. And it is not fair to say that the uncertainties and potential dangers associated with drug treatment are a "new risk" first "presented" by the progress of science in the mid-20th century. Those dangers have been with mankind for millenia, and have not gone unnoticed by government. It is at least as plausible that common law legislators *did* consider more aggressive medical regulation, but concluded that it would be inconsistent with the traditional rights of medical self-determination and self-defense. Thomas Jefferson likened

government interference with medicine to government meddling in religion, arguing that "[w]as the government to prescribe to us our medicine and diet, our bodies would be in such keeping as our souls are now. Thus in France the emetic was once forbidden as a medicine, and the potato as an article of food." *Notes on the State of Virginia,* Library of Am., Literary Classics of the United States, N.Y. 1984, p. 285.

II. THE DECISIONS RELIED UPON BY DEFENDANTS DO NOT ADDRESS THE FUNDAMENTAL RIGHT ASSERTED HERE

Appellees and the panel dissent have cited a number of cases that rejected patients' claims for access to medications in various circumstances. None of those decisions considered the fundamental right asserted by appellants.

Appellees rely on the Supreme Court's decision in *United States v. Rutherford*, 442 U.S. 544 (1979), and the Tenth Circuit's opinion on remand, *Rutherford v. United States*, 616 F.2d 455 (10th Cir. 1980). But the Supreme Court explicitly declined to address the constitutional issues in *Rutherford*, deciding only that there is no implicit *statutory* exemption from the FDCA for terminally ill patients. *See* 442 U.S. at 558-59 & n.18. The Tenth Circuit had held that "'the "safety" and "effectiveness" terms . . . have no reasonable application to terminally ill cancer patients,'" *id.* at 551 (quoting *Rutherford v. United States*, 582 F.2d 1234, 1236 (10th Cir. 1978)), a holding that would have "den[ied] the Commissioner's authority over all drugs, however toxic or ineffectual, for such

individuals," *id.* at 557-58. The Supreme Court rightly rejected that extreme interpretation of the statute, which would have allowed patients to take non-investigational drugs that the FDA had affirmatively determined to be unsafe. The Court also made clear that it viewed "effectiveness" review as rational in the context of terminally ill patients principally because such patients might *reject conventional therapy that could help them.* "[I]f an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible." *Id.* at 556. On remand the Tenth Circuit also rejected the constitutional claims only in the context of individuals selecting laetrile over conventional therapy. *See Rutherford*, 616 F.2d at 457.

Neither the Supreme Court nor the Tenth Circuit in *Rutherford* ever considered the issue presented here. The plaintiff in *Rutherford* was seeking a right to take anything he wished, regardless of whether he had other approved treatment options. Appellants in this case do not seek a right to take whatever treatment they wish, but only to access investigational drugs already approved by the FDA as suitable for clinical trials with human subjects, and then only if they have no other approved treatment options. The Supreme Court supported its reading of the statute in *Rutherford* by noting its holding would not "foreclose all resort to experimental cancer drugs by patients *for whom conventional therapy is*

unavailing," because of the statutory exemption for investigational use. 442 U.S. at 558 (emphasis added). And the FDA itself has distinguished *Rutherford* by observing that the Court "noted that application of the new drug approval provisions to therapies for terminal diseases did not foreclose resort to experimental drugs by patients for whom conventional therapy was unavailable." 52 Fed. Reg. 19,466, 19,473 (May 22, 1987); *see also* Batterman, 19 Hofstra L. Rev. at 205 (arguing that the Supreme Court's decision in *Rutherford* should "be limited to the question of access to experimental treatment for terminal patients where alternative approved methods are available.")

The other cases relied upon by appellees also involved drugs that had not cleared even the initial "safety" review necessary for investigational use in human subjects, drugs (like marijuana) that are prohibited by the criminal law because of the potential for recreational abuse, or patients who (as in *Rutherford*) were refusing to try conventional therapies that might help them. *See United States v. Burzynski Cancer Research Inst.*, 819 F.2d 1301 (5th Cir. 1987) (antineoplaston cancer therapy that failed to receive IND approval); *Mitchell v. Clayton*, 995 F.2d 772 (7th Cir. 1993) (upholding regulation requiring acupuncturist to obtain a license); *Carnohan v. United States*, 616 F.2d 1120 (9th Cir. 1980) (laetrile); *Garlic v. U.S. FDA*, 783 F. Supp. 4 (D.D.C. 1992) (drug denied approval by the FDA); *Smith v. Shalala*, 954 F. Supp. 1 (D.D.C. 1996) (patient refused approved

chemotherapy treatment); *Cowan v. United States*, 5 F. Supp. 2d 1235 (N.D. Okla. 1998) (goat serum antibody drug for AIDS that was denied IND approval by the FDA and placed on clinical hold); *Raich v. Ashcroft*, 248 F. Supp. 2d 918 (N.D. Cal. 2003) (refusing to make a medicinal use exception for federal regulation of marijuana, a Schedule I controlled substance).

III. THE FDA'S POLICY ARGUMENTS ARE PREMATURE AND UNPERSUASIVE

The FDA has offered a variety of public policy objections to expanding access to investigational drugs for terminally ill patients. Its *amicus* ASCO has indicated that it may share some of those concerns.[22] The short answer to most of these arguments is that they simply suggest that some government regulation of investigational drugs, even for terminally ill patients with no other options, will be narrowly tailored to compelling state interests. Appellants have never disagreed, and if the FDA and its amici have confidence in these arguments they will not be afraid to expose them to the light of narrow tailoring review. All of these issues should be considered by the district court on remand, and several raise factual questions that cannot be resolved in the present posture. Briefly:

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[22] ASCO claims to speak for all oncologists, but many practicing doctors disagree. In a 1999 survey of doctors "[n]early seven out of every ten respondents (69%) said that they favor changing federal law so that unapproved drugs and devices could be made available to physicians as long as they carried a warning about their unapproved status." *See* http://www.cei.org/gencon/003,02627.cfm. That is, of course, a much more expansive and radical position than appellants advocate here.

Patient safety and informed consent

As Justice Stevens explained in his concurring opinion in *Glucksberg*, the state's interest in protecting individual life "does not have the same force for a terminally ill patient faced not with the choice of whether to live, only of how to die." 521 U.S. at 746. Of course an investigational drug may shorten a terminally ill patient's life even further. The same is true of the radiation and chemotherapy most of these patients will have already been through. But by the time a drug is in Phase 2 or Phase 3 trials, the FDA has already made its initial screen for toxicity. It also has already certified that a clinical trial in several hundred or several thousand people is ethical, and that individual patients could reasonably decide to enroll in those trials and give informed consent. If the panel dissent were right that appellants' position would allow patients to make an "uninformed and involuntary choice," then the trials themselves would be unethical. The FDA would have been happy to let Abigail assume whatever risk Erbitux posed if she had gotten into the trial. Taking that risk / benefit (and philosophical) decision away from her just because she could not get into the trial is not narrowly tailored to any compelling state interest. It is misplaced and utterly incoherent paternalism, particularly in a society so committed to liberty that it routinely permits citizens to jump off bridges with parachutes, breathe bottled oxygen a hundred feet below the sea, and climb mountains under suicidally reckless conditions, just for fun.

Even for terminally ill patients, the government's compelling interest in protecting life and health might still justify prohibiting drugs that have already been shown to be ineffective or harmful. Appellants do not dispute the FDA's interest in restricting access to completely unapproved, non-investigational drugs like laetrile, which would include every variety of back-alley quackery. And, as the Supreme Court and Tenth Circuit recognized in *Rutherford*, if the patient has approved treatment options that *are* known to be effective, then permitting access to investigational drugs might harm the patient by inducing them to forgo conventional therapy. None of those concerns are relevant here.

The right recognized by the panel also says nothing about who decides whether a patient satisfies its requirements. If the FDA believes there is a substantial risk that patients and their doctors will lie about whether they are terminally ill or genuinely have no other alternatives, then some oversight or screening process might be reasonable. Of course that process would have to be designed in a way that is narrowly tailored to that compelling interest. The crushing paperwork requirements and multi-month delays associated with the current and proposed "treatment IND" process will not, appellants submit, ultimately withstand scrutiny. *See, e.g.,* 71 Fed. Reg. 75,151-52. The FDA admits that only about 650 people a year manage to take advantage of its single-patient IND procedures. *Id.* at 75,157.

Incentives to participate in trials

The FDA and ASCO have also suggested that a right of access to investigational medications could undermine incentives for individuals to sign up for regular clinical trials. That too is a red herring. Appellants have already conceded that an available clinical trial for the treatment the patient hopes to pursue would qualify as an approved treatment option sufficient to dispel any constitutional right of access to treatment outside of that framework, even if enrollment in the trial would create some risk of receiving placebo.[23] Regulations requiring the FDA to evaluate whether a proposed treatment use will interfere with enrollment of patients in ongoing clinical investigations, *see* 71 Fed. Reg. 75,153, therefore do not infringe the right at issue here. Appellants would also happily concede that (if properly implemented) such provisions would be narrowly tailored to a compelling state interest in protecting the trial process.

Appellants brought this lawsuit on behalf of patients who are unable to participate in clinical trials. The FDA concedes that "participation in a clinical trial may not be possible for many reasons," such as if the patient has "a stage of the disease different from the stage being studied" or has "failed on, or be[come] intolerant of, the active control in a randomized active-control trial," or if it is

[23] It is, however, rarely necessary to give sugar pills to cancer patients in order to establish a valid placebo control for a new drug trial. It is generally known what happens to various cancers when untreated, and historical patient files can serve as controls if properly randomized.

"geographically impossible for the patient to participate." *Id.* Allowing such patients to die in the name of protecting incentives to participate in the very trials they have fought, unsuccessfully, to join is perverse and irrational. If the FDA or ASCO are concerned that patients will lie or evade eligibility, then (as noted above) that might justify a review process. If they have some other danger in mind and can craft a regulation narrowly tailored to address it, then appellants may well be in complete agreement. Appellants yield to no one in their commitment to rapid scientific progress in cancer treatment. But FDA itself recognizes that treatment use can coexist with the clinical trial process.

Consumer protection

Appellants believe that the FDA's policy of not permitting drug companies to charge more than cost recovery for investigational drugs impermissibly burdens the fundamental right properly recognized by the panel. Surely a State could not, for example, circumvent the Supreme Court's holdings in *Griswold* and *Eisenstadt* by decreeing that contraceptives may not be sold at any price higher than cost—thereby driving all of the for-profit manufacturers from the market. A somewhat more liberal policy permitting patients to offer drug companies at least a modest and reasonable profit would help encourage them to participate in expanded access programs. Despite its earlier position with regard to standing in this case, the FDA clearly now agrees with the basic point that drug companies respond to incentives.

It has promulgated new regulations liberalizing and clarifying the rules about charging for investigational drugs because, in part, "FDA wants to encourage sponsors to make investigational drugs available to seriously ill patients who lack satisfactory alternative treatment and might benefit from those drugs," which is "potentially costly." 71 Fed. Reg. 75,170.

The government may have a compelling consumer protection interest in protecting the public from the marketing of drugs that have been proven ineffective, and in ensuring that drug companies do not take advantage of inequalities of bargaining power to charge outrageous prices. But the FDA's prohibition on the sale of IND medications at any price higher than cost is not narrowly tailored to any genuinely compelling consumer protection interest. Again, however, these issues should be considered on remand.

Insurance coverage and Medicare / Medicaid

ASCO's motion seeking leave to file makes the cryptic suggestion (at 4) that a victory by appellants "would disrupt current reimbursement practices of major third-party payers, including Medicare and Medicaid." FDA approval for the use in question, or a medical consensus about the efficacy of an "off-label" use for an approved drug as reflected in recognized compendia, is the nearly universal

prerequisite for coverage, including under Medicare and Medicaid.[24] Nothing about this case would change that. The FDA apparently does not believe that its own expanded access initiatives will disrupt reimbursement practices. If ASCO fears some more complex interaction with present policy language or reimbursement statutes, then that would (at most) be an appropriate subject for narrow tailoring scrutiny on remand.

CONCLUSION

The district court's Order should be reversed, and this case should be remanded for further proceedings.

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[24] *See, e.g.*, 42 U.S.C. § 1396r-8(k)(2), (k)(3), (k)(6) (defining covered Medicaid outpatient drugs as requiring FDA approval or inclusion in recognized compendia for "medically accepted indications"); 42 U.S.C. § 1395w-102(e)(i) (adopting Medicaid definition for Medicare Part D drug coverage); 42 U.S.C. § 1395x(s)(2)(Q) (recognizing Medicare Part B coverage for oral anti-cancer drugs approved by the FDA for a given indication); 42 U.S.C. § 1395x(t)(2) (further defining Part B coverage for anti-cancer drugs for off-label indications, to both require FDA approval and inclusion in recognized compendia or support by peer-reviewed clinical literature for non-approved indication); *Understanding the Approval Process for New Cancer Treatments*, National Cancer Institute, *available at* http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5 (discussing similar state laws regulating private insurers); *Q&A: Off-Label Drugs*, Association of Cancer, *available at* http://www.acor.org/clinical/offlabel.html#Anchor--Wh-62318 (same).

Dated: December 29, 2006

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CERTIFICATE OF COMPLIANCE

In accordance with Rules 32(a)(7)(B) and (C) of the Federal Rules of Appellate Procedure and Circuit Rule 32(a), the undersigned certifies that the accompanying brief has been prepared using 14-point typeface, proportionally spaced, with serifs. According to the word processing system used to prepare the brief, Microsoft Office Word 2003, the brief contains 13,965 words, exclusive of the table of contents, table of authorities, glossary, attorney identification, and certificates of service, compliance, and as to parties, rulings and related cases.

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CERTIFICATE OF SERVICE

I hereby certify that on this 29th day of December, 2006, two copies of the foregoing Brief of Appellants were served by hand delivery on the following:

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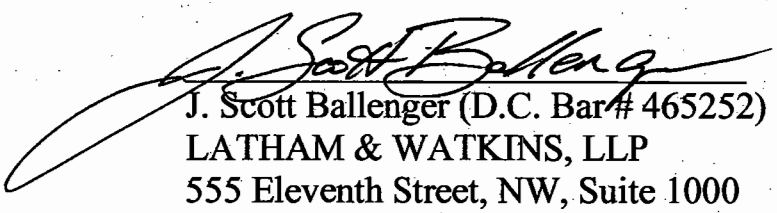

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INDEX TO STATUTORY ADDENDUM

UNITED STATES CODE
TITLE 21. FOOD AND DRUGS
CHAPTER 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT
SUBCHAPTER V. DRUGS AND DEVICES
PART A. DRUGS AND DEVICES

§ 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

* * *

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section;

or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

* * *

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section; and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including--

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that--

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

* * *

CODE OF FEDERAL REGULATIONS
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE
PART 312--INVESTIGATIONAL NEW DRUG APPLICATION
SUBPART A--GENERAL PROVISIONS

§ 312.7 Promotion and charging for investigational drugs.

* * *

(d) Charging for and commercialization of investigational drugs—

(1) Clinical trials under an IND. Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) Treatment protocol or treatment IND. A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under § 312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) Noncommercialization of investigational drug. Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.

(4) Withdrawal of authorization. Authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.

CODE OF FEDERAL REGULATIONS
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE
PART 312--INVESTIGATIONAL NEW DRUG APPLICATION
SUBPART B--INVESTIGATIONAL NEW DRUG APPLICATION (IND)

§ 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are as follows:

(a) Phase 1.

(1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

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§ 312.22 General principles of the IND submission.

* * *

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

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§ 312.34 Treatment use of an investigational new drug.

(a) General. A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.

(b) Criteria.

(1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) Immediately life-threatening disease.

(i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) May be effective for its intended use in its intended patient population; or

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(ii) For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(c) Safeguards. Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56) and the applicable provisions of Part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

(d) Clinical hold. FDA may place on clinical hold a proposed or ongoing treatment protocol or treatment IND in accordance with § 312.42.

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§ 312.35 Submissions for treatment use.

(a) Treatment protocol submitted by IND sponsor. Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall submit to FDA a treatment protocol under § 312.34 if the sponsor believes the criteria of § 312.34 are satisfied. If a protocol is not submitted under § 312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under § 312.34. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

(i) The intended use of the drug.

(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages.

(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:

(i) Informational brochure for supplying to each treating physician.

(ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.

(iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR Part 50.

(3) A licensed practitioner who receives an investigational drug for treatment use under a treatment protocol is an "investigator" under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR Parts 50 and 56.

(b) Treatment IND submitted by licensed practitioner.

(1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA 1571) meeting § 312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with § 312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.

(iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.

(v) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.

(vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) Agreement to report to FDA safety information in accordance with § 312.32.

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR Parts 50 and 56.

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§ 312.36 Emergency use of an investigational new drug (IND).

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23 or § 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. For investigational biological drugs regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, 301-827-2000. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, 301-827-4570. After normal working hours, eastern standard time, the request should be directed to the FDA Office of Emergency Operations (HFA-615), 301-443-1240. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.

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SUBPART H--ACCELERATED APPROVAL OF NEW DRUGS FOR SERIOUS OR LIFE-THREATENING ILLNESSES

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.