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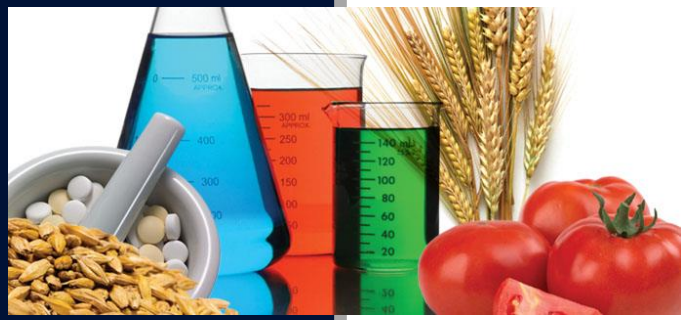

Food, Drug and Cosmetic Law Section Annual Meeting

January 25, 2018

Balancing the Ethical Duty of Zealous Representation with the "Greater Good" of Early Access to Investigational Drugs

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Agenda

Balancing the Ethical Duty of Zealous Representation with the "Greater Good" of Early Access to Investigational Drugs

- The Legal Landscape — Anne Pierson Allen, Esq.
- Ethical Challenges — Ilene Wilets, Ph.D.
- Ethical Duty to Legal Clients — David S. Weinstock, Esq.

The Legal Landscape

Anne Pierson Allen, Esq.

Expanded Access and Compassionate Use

- Both terms describe a scenario in which an investigational drug is used outside the setting of a clinical trial
- Three General Scenarios:
  - Individual Patient/Emergency Use
  - Intermediate-Size Patient Populations – (fewer than a new treatment IND/Treatment protocol but too many to continue filing single use submissions)
  - Treatment IND/Treatment Protocol (broader patient population)

Expanded Access General Criteria

- Patient has a serious or immediately life-threatening disease or condition;
- No comparable or satisfactory alternative therapy to diagnose, monitor, or treat;
- The potential benefits justify the potential risk and those risks are not unreasonable in the context of the disease;
- Use of the drug will not interfere with the investigation in support of marketing approval or otherwise compromise development of the drug; and
- Amendment to existing IND ("expanded access protocol") submitted by sponsor or
- New IND ("expanded access IND") may be submitted by physician for single patient

Individual Patients (21 C.F.R. § 312.310)

- Physician must determine that probable risk does not exceed that of the disease for the individual patient
  - Sponsor is often the physician, with regulatory obligations of sponsor-investigator
- FDA must deem that patient cannot obtain access under another type of IND or protocol
- Emergency use
  - FDA may authorize without written submission, followed by written submission within 15 working days
- Safeguards
  - Generally limited to single course of treatment
  - End-of-treatment report to FDA, including adverse effects
  - Monitoring not generally required

Intermediate-Size Populations (21 C.F.R. § 312.315)

- Demonstration of need for investigational drug
  - Drug being developed, but patient cannot participate in clinical trial
  - Drug not being developed (e.g., rare disease)
  - An approved or related drug is no longer marketed or not available (e.g., drug shortage with foreign version of drug)
- Sufficient evidence that drug is safe for proposed dose and duration relative to size of exposed population
- Preliminary clinical evidence of effectiveness or plausible pharmacologic effect
- Additional safeguards
  - Explanation of why drug cannot be developed or, if drug is being developed, why patients cannot be enrolled in a trial for the use
  - Monitoring, as well as annual report for review by FDA

Broad Populations: Treatment IND/Protocol (21 C.F.R. § 312.320)

- Drug is being investigated in clinical trial, or all trials have been completed
- Company is actively pursuing marketing approval
- Sufficient evidence of safety and effectiveness for the use
  - Serious Disease: Evidence from phase 3 or compelling data from phase 2 clinical trials
  - Immediately Life-threatening Disease: Evidence that drug may be effective for the use and would "not expose patients to an unreasonable and significant risk of illness or injury" (could consist of evidence more preliminary than phase 2 trials)
- Additional safeguards
  - 30-day wait period for FDA review, or earlier notification of FDA approval
  - Monitoring, as well as annual report for review by FDA

Role of Physician

- Only licensed physicians may administer or dispense an investigational drug under EA
  - Obligations of an investigator, including:
    - » Adverse event reporting to sponsor;
    - » Ensuring IRB review and informed consent; and
    - » Records, including accurate case histories and drug disposition
  - A licensed physician who also submits an IND for EA is considered a sponsor-investigator and must comply with the FDA requirements of both sponsors and investigators.

Role of Manufacturer

- Decide whether to provide the investigational drug under EA
- Decide whether to charge for the drug, pursuant to 21 CFR § 312.8
- EA for single patients
  - In response to a physician's request as the sponsor-investigator for access to an investigational drug for a single patient,
    - » Company is not required to provide the drug
    - » Company may decide to submit a protocol amendment to an existing IND for the single patient as the sponsor
    - » If company agrees to provide drug to physician as sponsor-investigator, company provides physician with Letter of Authorization to allow FDA to reference the company's IND

Role of Institutional Review Board (IRB)

- For single patient emergency use, the IRB will review the request for the physician using FDA guidelines for the Emergency Use of a Test Article. A full board meeting need not be convened.

  https://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm

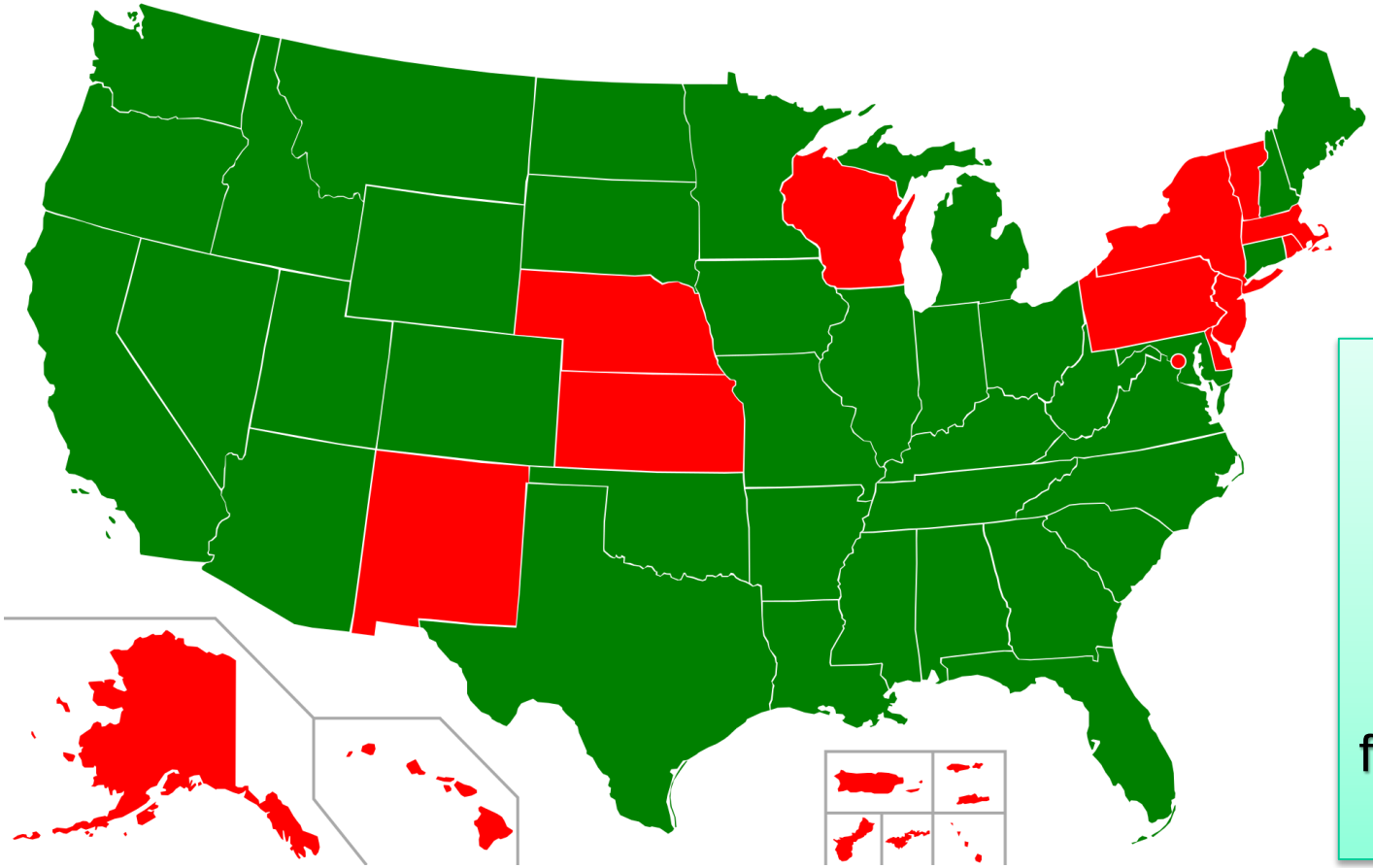
Role of Institutional Review Board (IRB)

- For all other Expanded Access options, the IRB requires a full new study application to be submitted for full board review.

  The application must include the following:
  - IND documentation from the FDA/drug manufacturer
  - Drug information via an Investigator's Brochure or a package insert
  - An informed consent document

- In non-emergent situations, treatment may not begin until the IRB has approved the Expanded Access protocol.

State Right to Try Laws



38 states have adopted Right to Try laws – but they vary from state to state

Green = Passed Law
Blue = Introduced Legislation
Red = Vetoed

FDA's 2016 Guidance

- "Individual Patient Expanded Access Applications. Form FDA 3926. Guidance for Industry." June 2016.
- "Expanded Access to Investigational Drugs for Treatment Use–Questions and Answers. Guidance for Industry." June 2016.
- "Charging for Investigational Drugs Under an IND–Questions and Answers. Guidance for Industry." June 2016.

FDA's 2016 Guidance

- Streamlines single patient expanded access
- New streamlined application is easily accessible on FDA website, with instructions
  - Only 2 pages and "45 minutes" of physician time
  - With appended Letter of Authorization, the form provides FDA with all of the information needed for agency to determine if requirements are met
- Only for use by licensed physicians to request single patient EA, including emergency use
  - All IND requests for FDA approval of EA for intermediate-size or large populations must continue to use Form FDA 1571

Federal Right to Try

- Senate passed S. 204 on August 4, 2017 ("Trickett Wendler")
- VP Pence and others are pushing hard for House to pass H.R. 878
- FDA Commissioner Gottlieb has raised concerns:
  - Fails to address primary reason most patients cannot obtain: companies have inadequate supply of drug
  - Sponsors and others providing drug to eligible patients would not be subject to FDA clinical trial, premarket approval, and labeling regs
  - Scope should be narrowed from patients with a "life-threatening disease or condition" to those facing "terminal illness"

Ethical Challenges

Ilene Wilets, Ph.D.

The Troubling Case of Josh Hardy

Josh Hardy, in the summer of 2013, when family members said he was at his healthiest. (Family Photo)

- Diagnosed at 9 months with Stage 5 malignant rhaboid tumors on his kidneys
- Aggressive cycles of chemotherapy , radiation and surgery throughout infancy and childhood put cancer in remission 3 times within a 7 year period.
- Disorder progressed to the point where a bone marrow transplant was indicated

The Troubling Case of Josh Hardy

- Following the bone marrow transplant, Josh developed a rare viral infection.
- His medical team suggested Brincidofovir, an experimental drug, as the only remaining option for Josh's survival
- Chimerix, the manufacturer of Brincidofovir, contended it could not dispense the drug to Josh while it was in ongoing clinical trials.

Josh Hardy Media Firestorm

Company denies drug to dying child

By **Elizabeth Cohen**, Senior Medical Correspondent
updated 2:57 PM EDT, Tue March 11, 2014

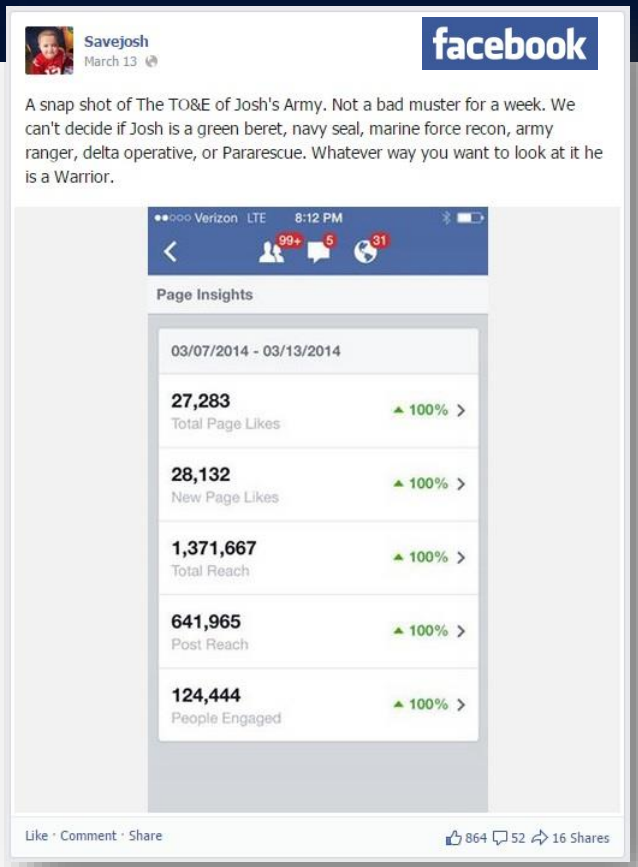
CNN

(CNN) -- In an intensive care unit in Memphis, a virus ravages the body of a 7-year-old who's in heart and kidney failure. He vomits blood several times an hour as his family gathers in vigil.

In a cabinet in Durham, North Carolina, there's a drug that could likely help Josh Hardy, but the drug company won't give it to him. They're adamant that spending the time to help Josh and others like him will slow down their efforts to get this drug on the market.

Helping Josh, they say, means hurting others.

twitter



The Washington Post

Health & Science

Crowdsourcing medical decisions: Ethicists worry Josh Hardy case may set bad precedent

A Bioethics Perspective

"You couldn't get a more troubling and impossible-to-resolve moral dilemma than this one," said Arthur Caplan, Director of the Division of Medical Ethics at New York University's Langone Medical Center.

"From the perspective of the public and future patients, it's best for the company to focus on getting the drug approved as soon as possible so that the largest number of people can be helped", Caplan said. "But from a patient's point of view, getting immediate access to the drug is what's important."

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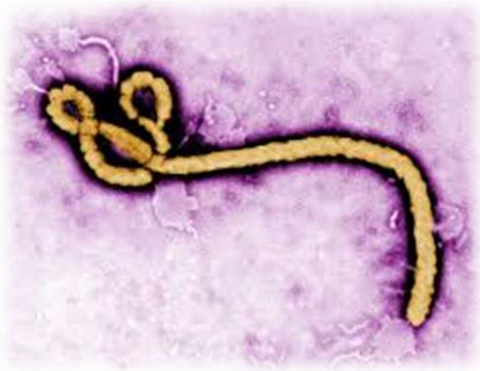
Ebola Raises More Questions



WHO Says ZMapp Is Ethical; Too Bad There's None Left

Small supplies of the drug bring up a whole host of other ethical dilemmas

By Mary Beth Griggs
SMITHSONIAN.COM
AUGUST 12, 2014

World Health Organization to Ethicists: Should We Use Experimental Ebola Drugs?

Treating two Americans with an untested drug for the deadly disease shifts thinking about ethics of use.

NATIONAL GEOGRAPHIC

Concerns Regarding Expanded Access

- The impact of expanded access on the scientific process
- The potential for injustices related to availability limitations
- Unrealistic optimism or therapeutic misconception

Ethical Duty to Legal Clients

David S. Weinstock, Esq.

Ethical Duty to the Client Company vs. Society

A “true” Right-to-Try (RTT) law would require a drug sponsor to manufacture and distribute a pharmaceutical so that the patient could exercise his/her “right” to take the product.

However, none of the current or proposed RTT laws make this requirement.

Ethical Duty to the Client Company vs. Society

Instead, they provide a mechanism which appears to permit the sponsor to circumvent the FDA regulations and procedures for Expanded Access

Joffe, Steven, and Lynch, Holly Fernandez, "Federal Right-to-Try Legislation – Threatening the FDA's Public Health Mission", *The New England Journal of Medicine* (January 12, 2018), accessed at:

http://www.nejm.org/doi/full/10.1056/NEJMp1714054#t=article

What is the Attorney's Responsibility

"The duty of a lawyer, both to the client and to the legal system, is to represent the client ***zealously*** within the bounds of the law, ..." [Emphasis added]

– Former New York versions of the Canons of Ethics

Saunders, Paul C., *Whatever Happened to 'Zealous Advocacy'?* New York Law Journal (March 11, 2011), accessed at:

https://www.cravath.com/files/Uploads/Documents/Publications/3272850_1.pdf

What is the Attorney's Responsibility

NEW YORK STATE RULES OF PROFESSIONAL CONDUCT (January 2017)

RULE 2.1.

Advisor

In representing a client, a lawyer shall exercise independent professional judgment and render candid advice.

In rendering advice, a lawyer may refer not only to law but to other considerations such as moral, economic, social, psychological, and political factors that may be relevant to the client's situation.

http://www.nycourts.gov/rules/jointappellate/ny-rules-prof-conduct-1200.pdf

Constitutional Issue 1

Preemption –

Doesn't the Supremacy Clause of the United States Constitution (Article VI, Clause 2) mandate that the FEDERAL Food, Drug and Cosmetic Act and Food and Drug Administration regulations preempt STATE Right-to-Try laws?

Attorney Ethical Issue 2

Does an in-house attorney have an ethical responsibility to "accept" his/her client's decision not to provide an IND under an Expanded Access plan, *even* if it would be approved under the FDA's regulations and processes and not under state(s) RTT laws?

Why Wouldn't the Company Want to Participate? ($$)

- Costs associated with EA Program:
  - Manufacturing drug products and companion diagnostic
  - Maintaining IND, labeling, database, etc.
  - Maintaining medical device quality program
  - Maintaining pharmacovigilance oversight
  - Continuing an open-label (open-ended!) extension study
- Potential products liability issues (notwithstanding informed consent and waiver of liability)
- Above finances not available to develop other pharmaceuticals

Hypothetical

Hypo Company has two drugs in development both for the same orphan indication: cancer of the pericardium (*i.e.*, the sac-like tissue that surrounds the heart)

There are no other marketed drugs for the prevention, treatment, or cure of this form of cancer which has a 100% fatality rate within six months of onset

Drug 1 – IND which failed its primary efficacy endpoints in a Phase 2 clinical trial

Drug 2 – IND which achieved its primary safety endpoints in a Phase 1 clinical trial

Both drugs require a companion diagnostic

Why Wouldn't the Company Want to Participate? (Ethics)

- Hypo Company's own clinical trials established *only* the safety of Drug 1 and Drug 2
- Neither product has had its efficacy established through successful clinical trials
- Even if a patient is faced with certain death since there is no other drug for his/her condition, does the company have a right – zealously pursued by its attorney – to decide against providing either or both Drug 1 and/or Drug 2 under an EA program?

Questions or Comments?

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