Off Label or On Target?
The Ethics of Investigational and Compassionate Uses

G. Kevin Donovan, MD, MA
Director, Pellegrino Center for Clinical Bioethics
Professor of Pediatrics
Georgetown University School of Medicine

Obligatory Disclaimer

"In the past 12 months I have had no relevant financial relationships with the manufacturers of any commercial products or providers of commercial services discussed in this CME activity."

Learning Objectives

The participants:

1. Will be able to differentiate between approved, unapproved, and extended access to drugs and devices.
2. Identify conflicts and situations that might make unapproved use desirable or necessary
3. Articulate the ethical conflicts that surround such usages.

Definitions

I. **Investigational:** subject to testing in clinical study or protocol to evaluate safety and/or effectiveness

II. **Drug**: achieves its primary intended purpose by clinical action or by being metabolized

III. **Device:** does not act as drug. Includes:

1. **"*non-significant risk*": contact lens, endoscopes, percutaneous catheters, infant jaundice monitors, crutch, wheelchairs**
2. **"*significant risk*": balloon dilation catheters, biliary stents, peritoneal dialysis devices, implantable penile prosthesis**

Definitions (continued)

Off label:

Use that is not included in the package insert (FDA approved labelling) for a drug or device – for indications, age of patient, or dosage.

Expanded access - "**compassionate use**"

Use of an investigational drug/device outside of a clinical trial by patients with serious or life-threatening conditions who don't meet criteria for a clinical trial

Off Label Usage in Pediatrics is Common

- 50-60% General Pediatrics
- 70% Specialty Pediatrics (GI, ICU, etc)
- 74% Infant-6 yo
- Frequent examples – acid suppressors, anti-TNF, anti emetics, laxatives

Reasons for Off Label Use
(Lack of Approval)

- Costs of research, testing and approval (and liability)
- Small pediatric market (10%)
- Fewer chronic pediatric illnesses
- No pediatric incentives for generic manufacturers
- Absence of FDA approval does not limit off-label usage.

Federal Legislation to Increase Drug Testing and Approval in Children

- ❑ Best Pharmaceuticals for Children Act
- ❑ Pediatric Research Equity Act
- ❑ NIH/NICHN support and solicitations (Pediatric Trials Network)

Good: 500 pediatric labelling changes
Bad: 50% of labelling still has no pediatric information

Ethical Challenges in Off Label Usage

I. Not regulated, no specific requirements for informed consent
II. May be standard of care, or truly investigational
III. Manufacturers prohibited from promotion (but article distribution of off-label uses OK)
IV. Off-label studies may be insufficient to determine efficacy, dosage, adverse effects
V. Physician knowledge of validity or absences of off-label drug uses is poor

"Off-Label" Issues
Possible Approaches

I. Require manufacturers to gather data on common or problematic off-label uses
II. Government evaluation and publication for common best and worst practices
III. Specialty societies, independent researchers, etc. be authorized to seek approval for off-label uses
IV. Drug newsletter and blogs pay special attention to publicize and evaluate evidence for off-label uses

Expanded Access/
"Compassionate Use"

Definition:

Use (outside of a clinical trial) of an investigational medical product, i.e. one without current FDA approval.

Reasons:

- No clinical trial
- Patient not eligible for current trial
- Drug or device desired for other than proposed indication
- No satisfactory alternatives - risk or drug/device commensurate with risk of disease

Expanded Access - Process

I. Sponsor submits application/protocol to FDA
   - Cannot be required to make product available
   - Cannot use data in later application for approval
   - Can charge for drug/device only under limited circumstances

Categories:

- For individual patients, including emergency use
- For intermediate-sized populations
- For widespread use

Case: Josh Hardy

- 7 yo cancer patient, s/p bone marrow transplant
- Systemic adenovirus, Tx with IV brincidofovir caused renal failure
- Physicians at St. Judes petition Chimerix for investigational p.o. form
- Chimerix declines
  - Only 50 employees (insufficient staff for massive FDA paperwork), limited inventory
  - 451 patients already given it via "compassionate use"
  - Cost to company = $50,000/pt
  - Further expanded access would delay bringing drug to market

Case: Josh Hardy (continued)

Outcomes:

- Massive bad publicity
- Death threats to CEO
- Chimerix creates 20-patient open-label study for Tx adenovirus in immunocompromised patients

The Case of Ebola

I. Dr. Sheikh Umar Khan – Z Mapp withheld – died
II. Nancy Writebol – treated with Z Mapp – survived
III. Dr. Kent Brantley – treated with Z Mapp – survived
IV. Spanish priest – treated with Z Mapp - died

Ebola Virus Disease

I. Treatment supportive therapy only
- Copious fluids + electrolytes
- Control of hemorrhage
- Treatment of renal failure

II. Protection: barrier methods, chloride disinfectant

III. Mortality
- 55—90% in African epidemic
- 2 of 10 treated in U.S.

Experimental Interventions

Treatment
- Blood plasma
- Z-Mapp
- Brincidofovir
- Favipiravir
- TKM-Ebola

Vaccines
- Glaxo-Smith-Kline/NIH
- New link genetics (Iowa/Canada) Merck
- Johnson & Johnson, Russia, Japan

Ethical Issues

- Should untested experimental treatments have been offered in this epidemic?
- When considering the scarce resources, the most pressing question: **who** should be treated?
- Was it unethical to use the few doses of Z-Mapp on American healthcare workers and the Spanish missionary priest and not Africans?

Ethical Issues (continued)

- Should untested experimental treatments be offered?
- Rationale for controlled trials vs. "compassionate use"
- Does acceptance reflect informed consent or situational coercion?

Arguments Against "Compassionate Use"

I. Inequality of access – squeaky wheels
II. Drug may be blamed for failures or adverse events jeopardizing its ultimate approval
III. Patients refuse clinical trials with placebo arms
IV. Limitations in stockpiled supply
V. Most innovative drugs from small companies with limited financial and staff resources
VI. Benefit may occur in only 10% of trials

Expanded Access – Compassionate Use A Way Forward?

I. "Right to Try" Laws (CO, LA, MO) – bypass FDA
I. FDA has now limited preconditions, cutting hundreds of hours of paperwork to 45 min.
II. Shorten time from study to approval?
III. Governmental funding to subsidize expanded access?
IV. Bioethics panel to make allocation decisions (Johnson & Johnson)