International Summit on Gene Editing
CAS/RS/NAS/NAM
December 2, 2015

Panel: Governance at the Institutional and National Levels: national regulatory frameworks

Barbara J. Evans, Ph.D., J.D., LL.M.
Director, Center for Biotechnology & Law
University of Houston Law Center
1-713-743-2993 • bjevans@central.uh.edu

Disclosures

No conflicts to disclose.

Speaker receives research funding from various public and non-commercial private sources.

Point 1

Question. Do current ethical and legal standards for human subjects research adequately address human gene editing, including germline editing?

Answer. They may have to do so. Gene editing is here now.

FDA's Research Regulations

Ethics regulation	
Informed consent	21 CFR pt 50
IRB/ethics board review	21 CFR pt 56
Conflict disclosures	21 CFR pt 54

Regulate unapproved *products* and significant-risk *uses*	
IDE investigational device	21 CFR pt 812
Device labeling, mfg, distribution	21 CFR pt 809
IND investigational new drug, incl. biologic drugs	21 CFR pt 312
INAD investig'l new animal drug	21 CFR pt 511.1

Is it a drug or a device? Both encompass items:

- Intended for use in the diagnosis, cure, mitigation, treatment of disease
- Intended to affect the structure or any function of the body of man

A device "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and … is not dependent upon being metabolized for the achievement of its primary intended purposes." FFDCA §§ 201(g), (h), 21 USC 321(g), (h)

→ At a micro level, is the chemical/mechanical distinction meaningful?

Products that meet the definition of device also meet the definition of drug, due to the broader scope of the drug definition, and "if a product is shown to meet both the drug and device definitions, the Agency generally intends to classify the product as a device." *FDA Draft Guidance (June 2011)*

An idea to consider

Characterizing gene editing instrumentalities as devices rather than drugs may allow better regulation of research involving germline gene editing and better control over off-label uses of approved gene editing products.

That is, conceive technologies like CRISPR-Cas9 as micro-scalpels and inserted DNA constructs as genetic prosthetics.

Why do this?

Different definitions of "human subject" in FDA's IND and IDE regulations

- People who receive somatic gene editing are "human subjects" who are protected by FDA's investigational new drug (IND) regulation.
- People who provide embryos or gametes for germline gene editing do not seem to qualify as "human subjects" under FDA's IND regulation.
- But they would be "human subjects" under FDA's investigational device exemption (IDE) regulations, which includes people "on whose specimens" an investigational device is used.

See definitions at 21 CFR §§ 312.3(b), 812.3(p)

Other potentially useful device provisions for editing rare genetic variants

Orphan drug

- fewer than 200,000 patients/year

Humanitarian Use Device/Device Exemption

- fewer than 4,000 patients/year

Custom device (e.g., orthodontic appliances)

- fewer than 5 units per year

Restricted device

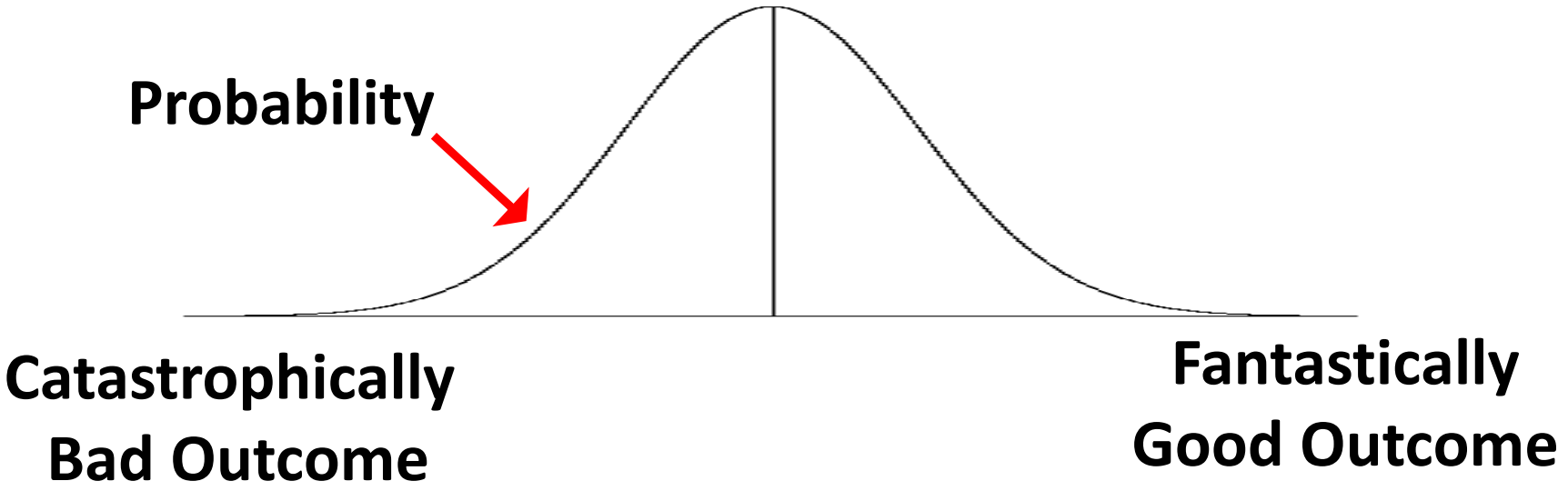
- approve with restrictions on distribution and use

Point 2

It is simplistic to think that some nations have "precautionary" regulatory frameworks while others have "permissive" frameworks.

Most real regulatory frameworks strike a balance between innovation and consumer protection by combining elements of both.

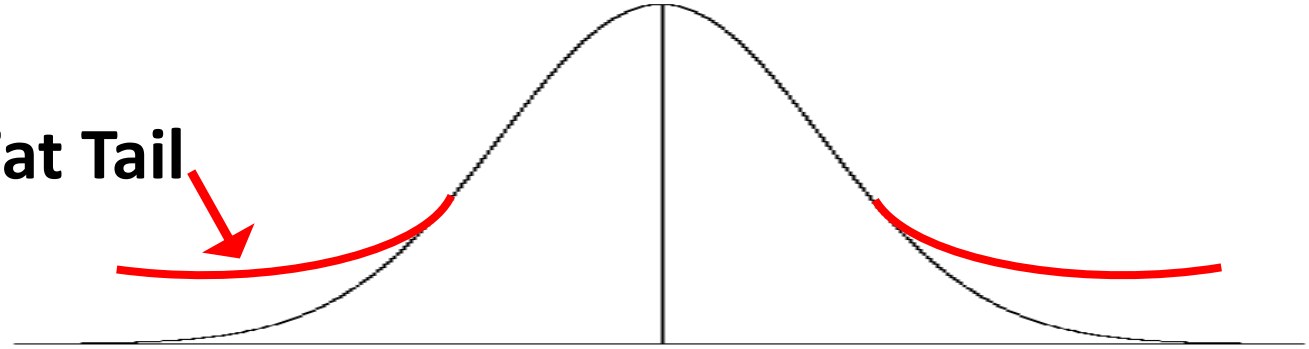
Risk exists when the probability of various outcomes can be quantified with fair confidence



Risks are tractable from a policy perspective if:

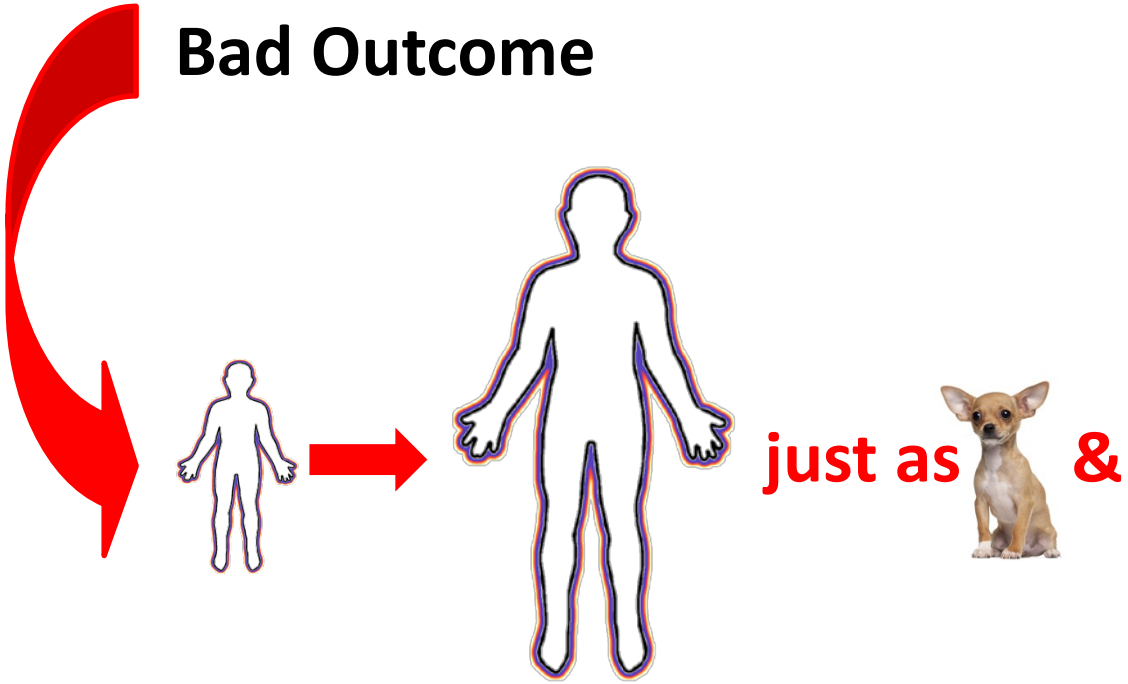
- Outcomes tend to cluster around the middle
- Upside and downside deviations seem equally plausible
- Extreme deviations seem unlikely

Uncertainty exists when probabilities cannot be quantified with any confidence

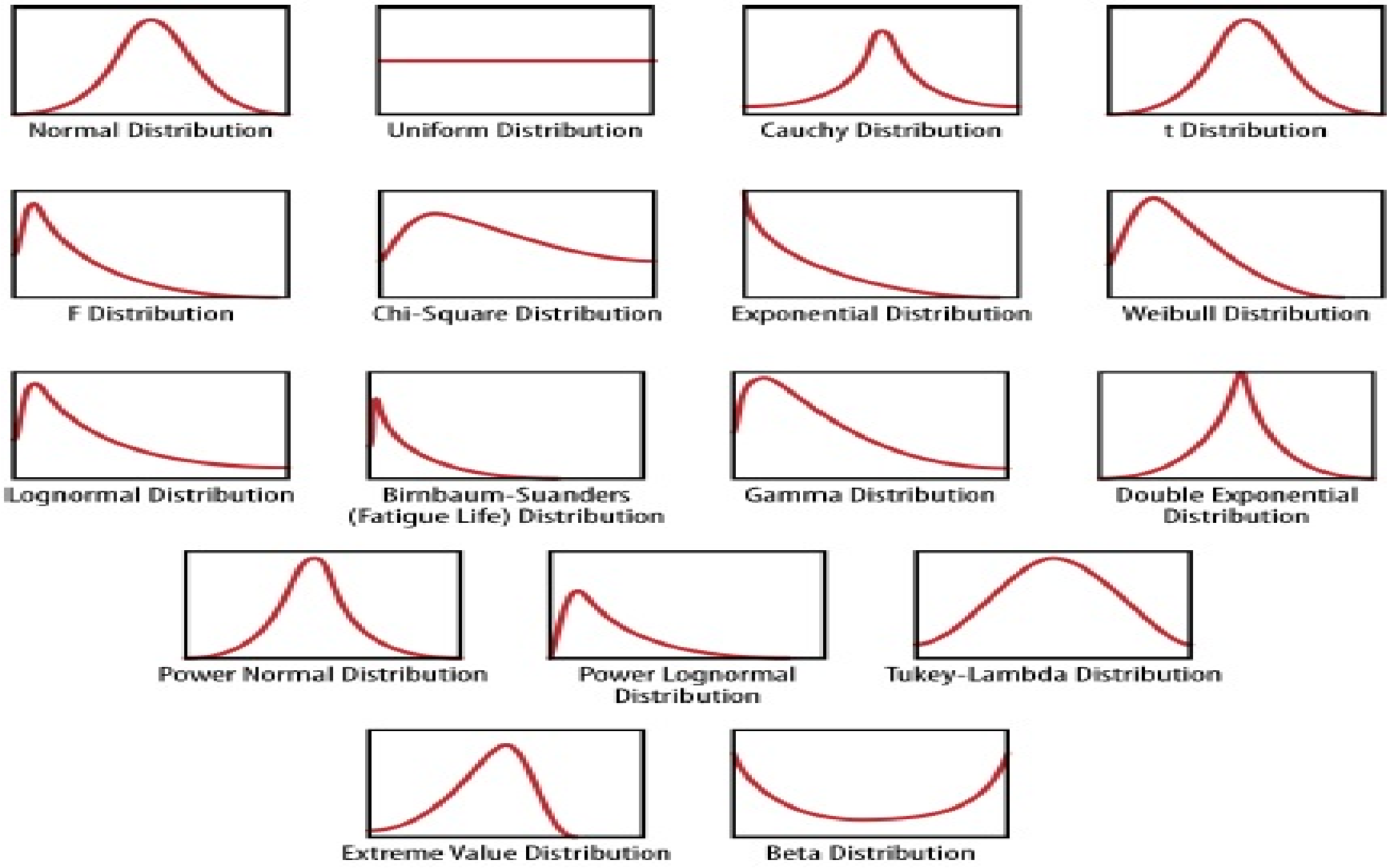


Catastrophically Bad Outcome

Fantastically Good Outcome



It may not even be possible to infer the general shape of the probability distribution



"In dealing with complex biological systems, some scientific uncertainty will always occur.

many countries believe it is appropriate to take ***precaution.***

there is, as yet, no international consensus on what *precaution* is"

Source: OECD, Report of the Working Group on Harmonization of Regulatory Oversight in Biotechnology (2000)

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence
b. Regulator burden to prove potential harms

Risk analysis, management, disclosure

α-MaxMin — weight both best and worst cases

MaxMin — pursue "least-bad" worst case

Arbitrary safety margins to address uncertainty

Evidence-forcing solutions to reduce uncertainty

a. Sponsor burden to develop prior evidence of safety
b. Facilitate cautious research to delimit uncertainty

Catastrophic precautionary principle – moratoria only for irreversible or catastrophic uncertainties

Wide moratoria – presume unquantifiable risks serious

Precautionary

Can we even agree what a “catastrophe” would look like?

Source: http://www.earthmagazine.org/sites/earthmagazine.org/files/1324689388/i-269-7d9-9-2.jpg

- Is it a catastrophe if patient harms pass to the next generation? If so, unedited genes are a catastrophe.
- I prefer a definition that highlights global impacts, e.g., destruction of an important food crop.

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence

b. Regulator burden to prove potential harms

Risk analysis, management, disclosure

α-MaxMin — weight both best and worst cases

MaxMin — pursue "least-bad" worst case

Arbitrary safety margins to address uncertainty

Evidence uncertainty

a. Spon ence of safety

b. Facili uncertainty

Catastroph moratoria only for irrevers or catastrophic uncertainties

It is unlawful to sell new drugs and many medical devices without prior FDA review

Wide moratoria – presume unquantifiable risks serious

Precautionary

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence

b. Regulator burden to prove potential harms

R analysis, management, disclosure

both best and worst cases

least-bad" worst case

ns to address uncertainty

Evidence uncertainty

a. Spon ence of safety

b. Facili uncertainty

Catastroph - moratoria only for irrevers e or catastrophic uncertainties

Wide moratoria – presume unquantifiable risks serious

Precautionary

FDA's GRAS presumption for genetically modified foods

It is unlawful to sell new drugs and most medical devices without prior FDA review

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence
b. Regulator burden to prove potential harms

Risk analysis, management, disclosure

α-MaxMin — weight both best and worst cases

MaxMin — pursue "least-bad" worst case

Arbitrary safety margins to address uncertainty

Evidence-forcing solutions to reduce uncertainty

a. Sponsor burden to develop prior evidence of safety
b. Facilitate cautious research to delimit uncertainty

ia only

FDA IND, IDE, and INAD regulations; EPA EUP and USDA APHIS permits for open-air testing of modified crops

erious

Precautionary

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence

b. Regulator burden to prove potential harms

Risk analysis, management, disclosure

α-MaxMin — weight both best and worst cases

MaxMin — pursue "least-bad" worst case

Arbitrary safety margins to address uncertainty

Evidence-forcing solutions to reduce uncertainty

a. Sponsor burden to develop prior evidence of safety

b. Facilitate cautious research to delimit uncertainty

Catastrophi- moratoria only

for irrev ertainties

Wide morato ble risks serious

FDA New Drug Approval,
Device Premarket Approval,
New Animal Drug Approval

Precautionary

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate

b. Regulator burden to pro

Risk a[nalys]is, managem[ent]

est and worst cases

ad" worst case

ddress uncertainty

educe uncertainty

a. Sponsor burden to develop prior evidence of safety

b. Facilitate cautious research to delimit uncertainty

Catastrophi[c] - moratoria only for irrev[ersible] ertainties

Wide morato[ria] ble risks serious

Precautionary

But: FDA presumes premarket clinical trial evidence reflects real clinical experience

FDA 510(k) clearance presumes substantial equivalence implies safe & effective; CLIA regulations presume certified labs will provide safe diagnostic tests

FDA New Drug Approval and Device Premarket Approval

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence
b. Regulator burden to prove potential harms

Ri k analysis, management, disclosure

MaxMin — weight bo

M in — pursue "lea

p prior evidence of safety

ch to delimit uncertainty

Ca principle – moratoria only for irreversible or catastrophic uncertainties

Wide moratoria – presume unquantifiable risks serious

Precautionary

FDA traditionally had few tools to require sponsors to conduct postmarketing studies and relied on mostly voluntary AE reporting

2007 FDAAA statute gave FDA new tools for active postmarketing surveillance and power to require postmarking studies & trials

Venturesome

Safety presumption – ignore unquantifiable harms

Rebuttable presumption of safety

a. Sponsor duty to generate ongoing evidence

b. Regulator burden to prove potential harms

Risk analysis, management, disclosure

α-MaxMin — weigh both best and worst cases

MaxMin — pur[illegible] "least-bad" worst case

Arbitrary sa[illegible] [illegible]ncertainty

Evidence-fo[illegible] [illegible]ncertainty

a. Sponsor [illegible]ce of safety

b. Facilitate cautious research to delimit uncertainty

RAC oversight/advice considers benefits and risks

Catastrophic precautionary principle – moratoria only for irreversible or catastrophic uncertainties

Wide moratoria – presume unquantifiable risks serious

Precautionary

Point 3

Be skeptical of widely held assumptions

The “science” of regulation is more precarious and uncertain than the science of gene editing.

Example: Harmonization is widely presumed to be good. *Is it really? If so, when?*

- **Consistency has merit in the face of irreversible or catastrophic externalities having global impact.** Inconsistent regulation subjects everybody to the lowest common regulatory denominator.
- **Absent shared global risks, regulatory diversity may offer advantages.** The "laboratory of nations" fosters innovation and rapid learning about the impact of striking different balances between innovation and precaution.
- **Does one size fit all?** E.g., editing of microbes, plants, animals in nature, animals in controlled settings, human somatic editing, human germline editing present different potential for global catastrophe.