



Investigational New Drugs, Clinical Testing, and Expanded Access/Right to Try

Michael S. Sinha, MD, JD, MPH

Research Fellow, Harvard-MIT Center for Regulatory Science
Affiliated Researcher, Program On Regulation, Therapeutics, And Law (PORTAL)

Adjunct Faculty, Northeastern University School of Law
Faculty Scholar, NUSL Center for Health Policy and Law



Reminders

<http://bit.ly/NUSLDrugLaw>

#NUSLDrugLaw on Twitter

2



Online Resources

- HarvardX massive open online course (MOOC), “#HarvardXFDA: The FDA and Prescription Drugs—Current Controversies in Context,” available at: <http://bit.ly/HarvardXFDA>.
- For the IP session, videos are available from the PennX MOOC, “Intellectual Property Law and Policy: Part 1,” available at: <http://bit.ly/PennXIP>.
- For the Opioids sessions, videos are available from the HarvardX MOOC, “The Opioid Crisis in America,” <http://bit.ly/OpioidX>.

3



Debates

- Debate 1: Prescription Drug User Fees (September 11, 2019)
- Debate 2: Off-Label Promotion (September 23, 2019)
- Debate 3: OTC Naloxone (October 16, 2019)
- Debate 4: Should the FDA be independent? (October 28, 2019)
- All students should come to class prepared to debate if called upon



DEADLINE CHANGE!

- Deadline for paper proposal **September 16th!**
- Describe legal arguments and policy solutions. Focus on how your proposal differs from existing published work.
- **TWO SAMPLE PAPER PROPOSALS NOW ON THE SYLLABUS PAGE**
 - Please follow this format when drafting your proposals



Public Comment Brief

- Review the docket announcement and related materials for the Proposed Rule, “Tobacco Products; Required Warnings for Cigarette Packages and Advertisements.” (Docket No. [FDA-2019-N-3065-0001](https://www.fda.gov/oc/2019-09-17-fda-proposed-rule-tobacco-products-required-warnings-cigarette-packages-advertisements)).
- Consult relevant legal, regulatory, and public health material to educate yourself about the context and implications for the proposed action.
- A structured “public comment” brief (5-6 pages) will be due before the start of class on Wednesday, October 2, 2019.





Current Events in Drug Law

#NUSLDrugLaw



Item #	1
Code	Resolution A-18 A-104
Title	Limiting the Scope of Involuntary Civil Commitment of Persons for Reasons Related to Substance Use Disorder
Sponsor	Michael Sinha, MD, JD, MPH
Referred to	Reference Committee A Mason Campbell, MD, MPH, Chair
HOUSE VOTE:	Adopted as Amended
Referred to:	Items 1, 3: Task Force on Opioid Therapy and Physician Communication Items 2, 10: Committee on Legislation Items 4, 8: MA AMA Delegation
Informational Report:	A-19
Strategic Priority:	Physician and Patient Advocacy
1.	That the MMS advocate for and advance research into any harms, benefits, and/or efficacy of any involuntary commitment solely related to substance use disorder. (S)
2.	That the MMS oppose involuntary civil commitment of persons for reasons solely related to substance use disorder without judicial involvement. (S)
3.	That the MMS work to advance policy and programmatic efforts to address gaps in voluntary substance-use treatment services. (S)
4.	That the MMS advocate that the American Medical Association oppose further expansion of authority to involuntary civil commitment of persons for reasons solely related to substance use disorder without judicial involvement in Massachusetts and nationally. (S)
5.	That the MMS advocate to limit the practice of involuntary civil commitment for reasons solely related to substance use disorder in Massachusetts in furtherance of health, ethical, and patients' rights imperatives. (S)
6.	That the MMS advocate that the American Medical Association work to advance policy and programmatic efforts to address gaps in voluntary substance-use treatment services. (S)

Baker's proposal to authorize medical professionals to hold a patient for up to three days for substance use treatment was not included in the compromise.



Current Events in Drug Law

#NUSLDrugLaw



Current Events in Drug Law

#NUSLDrugLaw



Current Events in Drug Law

#NUSLDrugLaw



Current Events in Drug Law

#NUSLDrugLaw



Current Events in Drug Law

#NUSLDrugLaw



Current Events in Drug Law

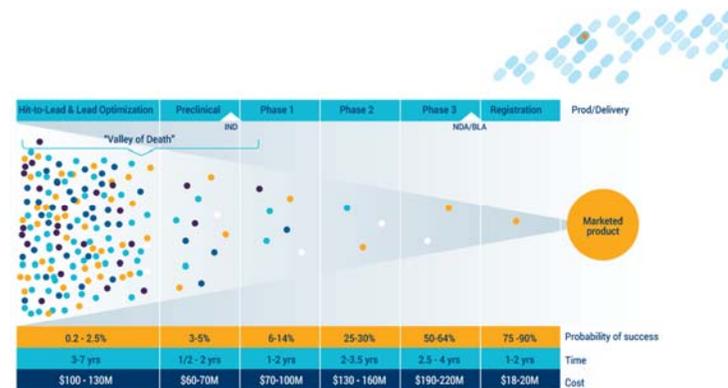
#NUSLDrugLaw



Current Events in Drug Law

#NUSLDrugLaw

The Process of Drug Development



“Valley of Death”

“The research process is complicated, time-consuming, and costly and the end result is never guaranteed. Literally hundreds and sometimes thousands of chemical compounds must be made and tested in an effort to find one that can achieve a desirable result.”

-- FDA: The CDER Handbook, The New Drug Development and Review Process

Source: Payne DJ, Gwynn MH, Holmes DJ, Pompilano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nat Rev Drug Discov*. 2007;6(1):29-40; Czaplewski L, Bax R, Chokie M, Dawson M, Fairhead H, Fischetti VA, et al. Alternatives to antibiotics-a pipeline portfolio review. *Lancet Infect Dis*. 2016;16(2):239-51.

Pre-Clinical Testing

- Before clinical (human) testing may begin on an investigational new drug (IND), substantial pre-clinical testing must be completed
- FDA does not directly regulate preclinical testing, but it indirectly shapes all preclinical work because drug sponsors will ultimately be accountable to the FDA for completing appropriate studies prior to initiating clinical trials



Pre-Clinical Testing

- This initial phase of testing requires at least two years but can last much longer
- Often includes:
 - Computer and animal modeling
 - Chemical analysis and manufacturing controls
 - Toxicity testing in laboratory systems and in animals
- Patent applications are often filed at this time on promising targets
 - First-to-file: a race to the patent office



Target Identification

- Basic human biology informs drug development
 - An understanding of how the body functions, both normally and abnormally
 - A role for the drug in preventing, curing, or treating a medical condition
 - Successful example: proton pump inhibition and GERD/reflux
 - Failing example: Alzheimer's drug trials and the amyloid theory of disease
- Sometimes, scientists find the compound quickly (*e.g.*, enantiomers)
- Often, hundreds or thousands may need to be screened
 - This may be why follow-on innovation is so common
- This process may also indicate ways of changing the compound's chemical structure to improve its performance (solubility, binding affinity, route of administration, etc.)



Synthesis and Purification

- Once an active pharmaceutical ingredient (API) has been discovered, the first step is synthesis and purification
- Natural product extraction usually cannot be accomplished at high concentration (though there are some examples, *e.g.*, heparin)
 - Thus, manufacturers must utilize synthetic organic chemistry or advanced biochemistry methods to replicate the compound affordably and at high volume
- Even if product was discovered by synthesis, scaling up production may require more efficient methods of manufacture



Pre-Clinical Testing

- (1) compiling existing nonclinical data from past *in vitro* laboratory or animal studies on the compound;
 - (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population;
- or
- (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans



Pre-Clinical Testing

- FDA will generally ask, at a minimum, that sponsors:
 - (1) develop a pharmacological profile of the drug;
 - (2) determine the acute toxicity of the drug in at least two species of animals, and
 - (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies



Investigational New Drug (IND)

- Once the target has met pre-clinical standards, the sponsor submits an investigational new drug application to the FDA
- This is required prior to any clinical testing of a new product – the process was created to avoid issues with interstate commerce, exempting a drug from being declared misbranded by permitting clinical testing across state lines
- INDs generally go into effect within 30 days if FDA takes no action
- FDA can put a “clinical hold” for various reasons, including concerns of significant risk of harm



Research Ethics

- Institutional Review Board: an independent committee, comprised of lay people as well as scientists, tasked with protecting the welfare of human research subjects
- Reviews a clinical protocol and exercises general supervision over the trial
- Assures compliance with local community ethical standards
- There are institutional IRBs and central IRBs:
 - Central IRBs may be more efficient, but don't allow individual sites to raise concerns relevant to their populations



Informed Consent

- Ensuring informed consent is the most important function of an IRB.
- A sponsor must "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."

-- FDCA § 505(i)(4)



Informed Consent

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.



Informed Consent

- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.



Early Meetings with FDA

- Perhaps the most important determinant of the success of the IND/NDA development process is the frequency and candor of meetings with FDA.
- Both experience and actual studies have determined that open communication with the agency is essential for an efficient and effective IND/NDA process.
- Increasingly, accelerated review pathways include required meetings and consultations with the FDA prior to NDA submission



Clinical Trials

21 CFR 314.126 requires "adequate and well-controlled studies"

- Phase I – often safety/dosing studies of healthy volunteers
- Phase II – early studies in small groups of patients with the condition
- Phase III – builds on phase II, more systematic assessment of safety and efficacy
- Phase IV – catch-all term for formal post-market studies
 - Not passive postmarket surveillance activities



Abigail Alliance

- What did you think of the case?
- Which argument persuades you more, the majority or the dissent?



Expanded Access

- Since 1938, FDA has consistently taken the position that an unapproved new drug may not lawfully be "commercialized" prior to approval.
- Patients generally cannot access an investigational drug outside of a clinical trial prior until it has been approved by the FDA
 - And under *Abigail Alliance*, no constitutional right to access investigational therapies
- Patients with rare diseases and no other good treatment options began to demand earlier access to the drugs, even as they were being tested in clinical trials
 - Drug companies often engage patient advocacy groups as stakeholders, to they are very aware of ongoing studies



Process of Expanded Access

- Also known as "compassionate use"
- FDA receipt of such requests is increasing
- Individual requests-the most common type-entails a physician making a special request to the FDA for a specific patient to be granted access to an investigational drug, such as under emergency circumstances.
- Intermediate-size groups of patients (in the tens to hundreds) who are similar in some way request early access to a developmental drug.
- Widespread use by large numbers of patients may occur after completion of a successful trial for an experimental agent, but prior to FDA approval and marketing.



Process of Expanded Access

- The FDA must, on a case-by-case basis, rule that the condition is "serious or immediately life-threatening," that "no comparable or satisfactory alternative therapies,]" exist, and that expanded access will not disrupt ongoing clinical trials.
- The FDA allows companies to bill insurance companies for direct costs associated with expanded access, though most manufacturers end up providing the drug free of charge
- To date, the agency has granted nearly every expanded access request, irrespective of category



Effect on Ongoing Research

- On paper, Expanded Access does not affect ongoing clinical trials
- In practice:
 - Expanded Access can limit enrollment of patients in trials, especially those with placebo controls
 - Safety risks found during Expanded Access cannot be used in considering FDA approval – no risk of jeopardizing clinical trials or product approval
- One concern relates to physician paperwork burden, though current paperwork takes 45 minutes or less to complete



Right-to-Try

- In spite of the relative benefits of Expanded Access (often granted, quick process), some libertarian activists and allied patient groups argued the FDA process was too bureaucratic and began advocating for the option to request experimental therapeutics directly from the pharmaceutical manufacturer (bypassing the FDA entirely)
- The Colorado legislature passed the first "right-to-try" law in 2014; after that, at least thirty-six other states have passed similar laws
- Congress passed the federal Right-to-Try Act in May 2018
- Shortly after its passage, the bill's primary sponsor, Senator Ron Johnson (R-WI), noted in a letter to the FDA Commissioner: "[the 'right-to-try' law] intends to diminish the FDA's power over people's lives, not increase it.

Right-to-Try

Box. Provisions of Senate Bill 204, The Right to Try Act of 2017²

- Applies to patients diagnosed with a life-threatening disease or condition who have exhausted treatment options and are unable to participate in a clinical trial.
- Provides an alternative to current expanded access procedures, which include US Food and Drug Administration (FDA) review of individual protocols and limit pricing of such drugs.
- Requires patient's informed consent and certification by the treating physician.
- Prohibits the certifying physician from being directly compensated by the drug manufacturer, but allows ownership of company stock and/or charging patient treatment fees.
- Applies to drugs for which a phase I clinical trial has been completed and are undergoing further testing but have not yet been approved by the FDA.
- Prohibits the FDA from using outcomes data to adversely affect approval or review of the drug unless the Secretary of the Department of Health and Human Services deems that such data are "critical to determining the safety of the eligible investigational drug" or the sponsor requests its use.
- Immunizes from liability manufacturers, physicians, and pharmacies (as long as conduct is not reckless or willful misconduct, gross negligence, or an intentional tort).
- Affirms manufacturers, prescribers, and dispensers are able to not provide access to an investigational product.

Right-to-Try

Table. Comparing the Text of Expanded Access Regulations and Federal Right to Try Act

	Expanded Access	Right to Try
Patients with serious conditions eligible	✓	
Patients with life-threatening conditions eligible	✓	✓
Exhaustion of approved treatment options	✓	✓
Consideration of clinical trial eligibility	✓	✓
FDA authorization of access	✓	
IRB authorization of access	✓	
Specified content of informed consent	✓	
Requirements for investigational labeling	✓	✓
Restrictions on promotion	✓	✓
Restrictions on charging by sponsor	✓	✓
Completed phase I testing		✓
Active development ongoing		✓
Immunity from liability		✓
Specification of acceptable use of clinical outcome		✓
Safety reporting to sponsor	✓	
Rapid safety reporting to FDA	✓	
Annual safety reporting to FDA	✓	✓
Public posting of information by FDA		✓
Sponsor compelled to provide access		✓
Insurers compelled to reimburse		✓

Questions

- What do you think of these programs?
- Do you think Right-to-Try is likely to be successful? Why or why not?

Any questions?

Dr. Sinha: m.sinha@northeastern.edu or michael_sinha@hms.harvard.edu
TA: Abby Fletes, fletes.a@husky.neu.edu