

A Science Based Regulatory Framework to Ensure “Healthy” Innovation to Improve Outcomes for Patients

Submission to the United Nations Secretary-General’s High Level Panel
on Access to Medicines

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Summary

The goal of medical innovation is to help patients live longer or live better. Therefore new technologies should provide added benefits over available therapies for the patients at an affordable price, with access to all. Current regulatory practice promotes developing interventions that are similar or in some cases even worse than current therapies, putting quantity and speed of bringing new products to the market before evidence of their benefit. The result in a wasteful innovation process, putting patients at risk, leading to unnecessary health expenditures, diverts resources from true public health innovation, and undermines the right to health and to the benefits of scientific progress.

In order to advance human rights and public health, and address possible inconsistencies with trade and commercial interests, it is crucial to ensure that only therapies with evidence of added benefits for the patients are being developed and approved. To that effect, we need a regulatory framework in which medical innovation is redefined to focus on benefits to patients, in particular and not mutually exclusive: improved effectiveness, decreased adverse effects, improved convenience, and/or decreased costs. Taking the specific example of infectious diseases, this submission outlines concrete proposals for regulatory reform that would refocus R&D incentives and requirements towards delivering patient-centered therapeutic advances that address unmet health needs.

Introduction

The current development process of medical technologies has focused on speed defining “innovation” as development of new technologies, without demonstration of added benefits. Current regulatory structures in the US and Europe place incentives on developing interventions similar or somewhat worse than current therapies, placing quantity over quality and speed over evidence. The end result is products that do not last in the marketplace. For example, the need for interventions with improved efficacy to address the problem of antibiotic resistance is well documented.¹ However current regulatory incentives are not designed to develop drugs with added benefits. Almost half of antibiotics approved in the US since 1980 have been discontinued from the market not because of antibiotic resistance but because of poor sales compared to older drugs or safety/efficacy issues discovered after approval despite lack of evidence of added benefits prior to approval.² The current political climate also has favored legislation that promotes less evidence, unclear benefits, prolonged exclusivity and patent rights and increasing prices.^{3,4}

The area of infectious diseases and developing new therapies to treat infections (both antibiotic resistant and susceptible infections) highlights how incentives have placed a focus on interventions without added benefits, placed current patients at risk, and not taken into account basic ethical research standards.

This proposal outlines how the current system can be improved by defining innovation as developing health technologies with clear added benefits for the patients, with infectious diseases as an example.

Dr. Maxwell Finland, the first President of the Infectious Diseases Society of America pointed out our obligations to patients to develop and prescribe better therapies:

“We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified.” ⁵

Background

The initial development of drugs was based on developing products with added benefits over the prevailing standard of care.⁶ However, over time the incentives in drug development have shifted to facilitate developing products without added benefits, or whose added benefits are unclear because of insufficient study, or outcomes that do not directly measure how patients feel, function or survive.⁷

Regulatory agencies in the US and Europe have increasingly relied on test tube data, animal studies, and post-hoc pharmacokinetic/pharmacodynamics subgroup analyses as the basis for approval, despite lacking evidence that such data predicts benefits for patients.⁸ Regulatory agencies have been pushed by the pharmaceutical industry to accept “smaller datasets” and clinical data in patients who already have effective therapies in order to gain market approval without added benefits in the patients whose unmet medical needs remain unaddressed.⁹ Indeed regulatory agencies have published articles in the medical literature agreeing with industry points of view.¹⁰ Regulatory agencies have published guidances (which are not law nor legally binding) promoting drugs without demonstrated benefits as “innovation” and good for public health despite a lack of evidence of benefits.

The end result is a system that approves medical technologies based on presumptions and “potential” rather than actual benefits, and that puts current patients in harms way for some putative unproven and unstudied “benefits” in groups of patients that are not defined or not studied. As stated previously, almost half of antibiotics approved in this way have been discontinued from the market, not by regulatory agencies but by the sponsors who marketed them.

The current political climate has also contributed to the incentives to develop products without added therapeutic value. The 21st Century Cures Act in the US promotes development of new drugs based on surrogate endpoints that are not direct measures of patient benefit, smaller datasets and presumptions of benefit without evidence. The Get Antibiotic Incentives Now or GAIN Act passed in the US in 2012 is the first FDA incentive program to not require evidence of added benefit in order for a new drug to obtain expedited review and approval, and to obtain extended periods exclusivity once approved. The only thing required is test tube evidence that a new drug has biological activity against one of the organisms from an exhaustive list of human pathogens that includes almost all pathogens that cause human disease. Even organisms that have not developed resistance over 80 years,

such as streptococci to penicillin, are included on the list. Such broad incentives do not focus resources on those products most likely to improve patient outcomes.

In conclusion, the current regulatory framework favors expending tremendous amounts of resources on products without demonstrated added benefits for patients, while increasing the costs of healthcare and thereby decreasing access to valuable medicines.

A comprehensive regulatory framework to ensure improved outcomes for patients

A science-based regulatory framework is needed that ensures that only therapies with evidence of added benefits for the patients are being developed, expedited and approved. New drugs alone, especially if not studied properly, will not only fail to address the problem but may make it worse since ineffective drugs harm public health as well as waste resources that could be put to developing better therapies. We propose a comprehensive set of suggestions to help patients and develop better therapies:

1. Defining Innovation Based on Patient Outcomes

The dictionary defines innovation as “a *new* method, product or idea.”¹ However, in order to benefit patients, innovations should be better than current alternatives, not just new. Being a “new option” is not sufficient to justify administration of experimental interventions to patients, speeding of regulatory approvals, or increase costs.

Innovation should be defined in terms of benefits to patients into one of four categories that are not mutually exclusive:

1. **Improved effectiveness** – medical technologies that improve how patients feel, function or survive compared to current best available technologies, not simply better than placebo.
2. **Decreased adverse effects** – medical interventions that have fewer adverse effects than current available therapies without substantial loss of effectiveness. An ineffective medical technology with fewer adverse effects or a new medical technology with fewer adverse effects but which

¹ <http://www.merriam-webster.com/dictionary/innovation>

increases mortality/morbidity in serious and life-threatening disease is not beneficial to patients

3. **Improved convenience** – medical technologies with improved convenience that results in decreased adverse effects or improved effectiveness, not minor changes such as once daily vs twice daily administration with no impact on patient outcomes.
4. **Decreased costs** – new medical technologies that decrease the overall costs of care.

2. Establishing a comparative effectiveness standard such that new medical technologies should meet one of the four criteria for true innovation. Current US FDA regulations state there is no comparative effectiveness standard and that a new drug only has to be better than placebo to receive marketing approval. However, despite a Federal Register notice from 1995 establishing that there is indeed a comparative effectiveness standard for life threatening disease where effective therapy exists this standard has been ignored. To justify expenditures on new product development as well as medical care a comparative effectiveness standard is needed and should be required.

3. Requiring expanded access programs for all drugs and biologics under any expedited review programs for drugs with live-saving potential: Patients who wish to gain access to experimental therapies and who wish to take an informed risk for themselves should have access to these drugs. Drug sponsors often refuse access to experimental medications¹¹ and should be required to have such programs under existing expanded access programs for all patients who do not qualify for ongoing clinical research studies. These programs were developed during the early years of the HIV epidemic so that patients could obtain access while the new therapies continued to be evaluated in adequate and well-controlled studies prior to widespread marketing. Such programs have already been streamlined, including rapid distribution and efficient Institutional Review Board (IRB) review to that patients can obtain access to experimental therapies.² The current program allows companies to recoup costs. If companies claim their products save lives then the way to address access is not approving interventions based on insufficient evidence but to improve access while trials to demonstrate the hypothesized benefits are ongoing.

² US Food and Drug Administration. Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)
<http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/accesstoinvestigationaldrugs/ucm176098.htm>

4. Studies to show improved outcomes in life-threatening diseases should be performed in patients who have an unmet medical need, not by putting current patients who have effective and safe current therapies at risk:

Expedited review programs based on less data should focus only on therapies that have demonstrated added benefits for patients. The ethical conduct of clinical research requires that studies be done in patients who might benefit from the test therapies. The current paradigm of approving drugs, especially antibiotics, is based on studies of drugs without added effectiveness performed in patients who already have safe and effective therapies and extrapolating results to unstudied types of patients. This is scientifically invalid and puts current patients in harms way without benefit. Patients who have current effective therapies should not be asked to accept more risk, as the risk-benefit decision in patients who do not have effective therapies is different than in patients who have effective and safe therapies. Therapies with substantial toxicity may be acceptable if they are life saving in patients who have no effective therapies. Drugs with increased toxicity are not acceptable in patients who already have effective and safe options. So-called “non-inferiority” studies ask the wrong question in the wrong types of patients.

5. Outcomes of clinical studies in patients should demonstrate benefits on patient centered outcomes such as decreased deaths and/or decreased disability in patients:

Since patients die or experience irreversible disability with serious disease, the outcomes in studies should be decreased deaths or decreased irreversible disability for patients. Surrogate endpoints are often unreliable yet continue to be used despite evidence that they do not predict benefits on helping patients live longer or live better. Direct patient centered outcomes should be used preferentially in acute diseases where the actual patient outcome can be measured in short period of time. Drugs that are marketed as “life saving” should actually be shown to save lives in adequate and well-controlled studies in patients. FDA’s own guidance on expedited approval programs states:

“Accelerated approval [based on surrogate endpoints] is generally less useful in more acute disease settings in which therapy is intended to provide a more near-term clinical benefit. In such settings, even if there are potentially predictive surrogate endpoints or intermediate clinical endpoints, there may be little or no time advantage for studies evaluating a surrogate or intermediate endpoint compared to studies evaluating the intended clinical benefit.”³

³ US Food and Drug Administration. Guidance for Industry. Expedited programs for serious conditions - drug and biologics.

Approval for chronic diseases based on outcomes that are not patient centered, should include a “sunset provision.” If confirmatory studies based on patient centered outcomes like decreased deaths are not done within a specified amount of time then approval should be automatically withdrawn. Companies should be required to keep open expanded access programs while further work is done to gain full approval.

6. Studies should be adequate and well-controlled, done in patients with the well-defined serious and life threatening disease under study, and not based solely on test tube tests, animal models or mathematical modeling:

Recent antibiotic studies have shown increased deaths or decreased cures in patients who received new antibiotics compared to older drugs already proven safe and effective in treating serious infections. These new drugs had promising test tube tests, animal models and mathematical modeling but they still resulted in worse outcomes for patients. Therefore concerns about the use of test tube tests, animal models and mathematical modeling are not merely theoretical but have resulted in real harms for patients who already have effective therapies. This type of preliminary information is not “confirmatory evidence”. Increased deaths have occurred more often in the sickest types of patients. Since patients with disease due to resistant pathogens tend to be older, sicker, have more concomitant disease and receive more medications, they are most likely to be harmed by ineffective drugs. Doing studies to evaluate whether a new drug is a little less effective (“noninferior”) in patients who are relatively less sick with disease due to susceptible organism and then extrapolating improved benefit to unstudied types of sicker patients with resistant pathogens is not logical or scientifically supported by these same studies showing harm in sicker patients. FDA has several warnings on it’s website concerning these drugs.⁴

7. Focusing studies on well-defined patient groups who may benefit will

allow for smaller studies: The number of patients needed to show a test intervention is more effective is based on how much more effective the new therapy really is: therapies with greater effectiveness need a smaller sample of patients and less effective therapies require a greater number of patients to study. Prioritization should be given to the most effective interventions, and accepting “limited datasets” for less effective drugs will only hide their lack of effectiveness. The earliest studies

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

⁴ FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning.

<http://www.fda.gov/drugs/drugsafety/ucm369580.htm>

FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia.

<http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm>

in infectious diseases in patients who lacked effective therapies required few patients because the drugs were highly effective in decreasing deaths in the studied patients.⁵ The size of a clinical study also has ethical implications for clinical research. The Institute of Medicine monograph on Small Clinical Trials points out:

“A critical aspect of clinical trial design is determination of the sample size needed to establish the feasibility of the study (i.e., sufficient statistical power). The number of participants in a clinical trial should always be large enough to provide a sufficiently precise answer to the research question posed, but it should also be the minimum necessary to achieve this aim. A proposed study that cannot answer the question being asked because the necessary sample size cannot be attained should not be conducted on ethical grounds. That is, it is unacceptable to expose patients or research participants to harms even inconveniences if there is no prospect that useful and potentially generalizable information will result from the study”⁶

8. New therapies can only be studied and used in practice with appropriate diagnostics: We need diagnostics that identify patients with a specific disease, as well as select patients who will benefit from specific new therapies. Empirical therapy (i.e. based on clinical suspicion) as routinely used with antibiotics exposes patients to excess harm. For instance it has been suggested that over 50% of people treated with anti-malarials do not have malaria. Approving drugs based on “limited datasets” and then using the drugs widely without ability to focus therapy on patients who benefit will also result in excess harm. Currently there is no incentive for drug companies to develop diagnostics since lack of appropriate diagnosis in noninferiority studies makes a new drug more likely to appear “noninferior” to an older effective agent. Empirical usage also spurs increased sales and increased profits. Any incentives for new drugs should be limited to those drugs that can define the patient characteristics of those who benefit and diagnostic testing in real world clinical practice that allows for selection of patients who benefit from new interventions.

⁵ Colebrook L, Kenny M. Treatment of human puerperal infections, and of experimental infections in mice, with prontosil. *Lancet* 1:1279-1286.

⁶ Institute of Medicine. Small Clinical Trials: Issues and Challenges. <http://www.iom.edu/Reports/2001/Small-Clinical-Trials-Issues-and-Challenges.aspx>

9. **Clinical trials transparency is needed to better inform patients, clinicians and drug developers:** Complete release of all clinical trials and preclinical information is needed. We can learn from both successes and failures of previous development programs to avoid repeating past mistakes. Clinicians should be able to access all information about drugs approved through both expedited and standard reviews in order to assess how the study design affects the reliability of the study results and to evaluate how the results apply to their particular patients.

10. **Regulatory labeling of new drugs should accurately reflect the benefits and harms and the types of patients studied, how clinicians should select those patients and the information used as the basis for approval:** Regulators do not regulate the practice of medicine but they do regulate what drug companies can advertise to practicing clinicians. Drug companies should not be allowed to advertise that their drugs are safe and effective in patients with a specific disease unless they have performed adequate and well-controlled studies in those patients. Clinicians are often forced to make treatment decisions without evidence not because we wish to do so but because the evidence is not available. Regulatory approval of new drugs based on assumptions from test tube results, animal models and mathematical modeling removes any incentive for drug companies to do appropriate studies in patients with resistant disease. Regulatory labeling informing patients and clinicians that a drug has not been studied properly does not help either patients or clinicians, and reserving a drug for those in whom the benefits outweigh the risks requires evidence about which patient experience those benefit and harms. Off-label promotion of drugs for diseases eliminates any incentive for companies to perform adequate and well-controlled studies and should be barred.

Regulatory labeling for antibiotics should remove statements instructing clinicians to administer antibiotics when infections are “suspected”. Rather than focusing usage of antibiotics, this allows drug companies to advertise drugs for empirical usage. What clinicians need is better diagnostics to focus usage so new therapies are prescribed to patients who actually need them and withheld them from patients who do not need them.

FDA labeling for any drug approved under expedited pathways should include wording that the drug has not been shown to be effective for diseases not studied.

11. **Stewardship of drugs, specifically antibiotics, and tracking of post-marketing use and adverse effect needs to accompany any program for approval whether expedited or not:** We need information on how and when drugs are used in both animals and human, what they are used for and how much is

used. Appropriate stewardship programs are needed to use drugs appropriately, especially with antibiotics where the US Centers for Disease Control data shows antibiotics are still used inappropriately in both inpatient and outpatient settings.⁷ Regulators should require a Risk Evaluation and Mitigation Strategies (REMS) that can take various measures to ensure appropriate use. These measures might include limiting prescribing and dispensing to certain trained providers or certified institutions, requiring administration in specific healthcare settings, or enrolling treated patients in a registry for monitoring follow-up outcomes.

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⁷ Centers for Disease Control and Prevention. Improving antibiotic use among hospitalized patients. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6309a4.htm?s_cid=mm6309a4_w

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