The 21st Century Cures Act: can the regulatory framework survive the "cures"?

Pode o arcabouço regulatório sobreviver ao 21st Century Cures Act?

¿Puede el marco regulatório sobrevivir al 21st Century Cures Act?

Claudia Garcia Serpa Osorio-de-Castro [1]
Rosângela Caetano [2]
Vera Lúcia Edais Pepe [1]

[1] Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.
[2] Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brasil.

Correspondence
C. G. S. Osorio-de-Castro
Departamento de Políticas de Medicamentos e Assistência Farmacêutica, Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz.
Rua Leopoldo Bulhões 1480, Rio de Janeiro, RJ 21041-210, Brasil.
claudiaosorio.soc@gmail.com

In 1963, Edward Lorenz proposed a theory, which has now entered into lore, that the ripples in the air produced by the fluttering of a butterfly's wings may cause a hurricane on the other side of the planet.

In July 2015, the House of Representatives of the United States Congress approved an act that considerably alters the USA's regulatory framework. The act, known as the 21st Century Cures Act ("*an act to accelerate the discovery, development, and delivery of 21st Century cures, and for other purposes*" [1]) is now to be examined by the Senate. Both the Democratic and Republican parties worked jointly to pass this legislation.

The act is undergoing scrutiny from the academic community in the USA and elsewhere [2], because of arguments that it may diminish the authority of the Food and Drug Administration (FDA). Opinions on the act diverge between those that see its measures to promote innovation as insufficient and those that consider the act a setback to health protection because it undermines the importance of the assessment of efficacy and safety of medicines and other health technologies [3]. Unforeseen consequences to the international regulatory machine may, however, not only be detrimental, but permanent, considering the FDA's worldwide influence on regulatory affairs.

Specific aspects of this new legislation must be discussed because of their implications which, in the name of flexibility and speed, may compromise a regulatory framework that took many years to refine and undermine the scientific and ethical bases for the approval process of health technologies.

One particular aspect is the criticism of the randomized controlled clinical trial (RCT) as a gold standard for efficacy. The act states that the approval process should consider innovative statistical methods, such as Bayesian methods of data analysis for medicines, and design strategies other than RCTs, such as non-clinical studies, small and short-term trials (for devices), and evidence from clinical experience, such as observational studies, therapeutic use, patient registries and clinical case studies [4].

This becomes particularly worrying when, of the 188 new drugs approved by the FDA between 2005 and 2012, 36.8% were approved based on a single pivotal trial. Additionally, 10.7% were not randomized and 20.5% were not double blind. The median number of patients per pivotal trial was 760 and more than two thirds of new drugs were approved by studies lasting 6 months or less, a problem for medicines intended for chronic use [4,5]. From 2005 to 2014, median assessment duration was 300 days and priority review procedures took 243 days [6]. From these data we may

surmise that the FDA procedures have not been especially slow or overzealous.

Drug approvals for serious infectious disease may be granted without traditional clinical trials, in "life-threatening" situations for patients with "unmet medical need". For this, the legislation rules the use of small or short-term studies, non-traditional efficacy data, especially non-clinical and pharmacokinetic data, Phase II studies, among others. However, additional trials to verify outcomes produced by these alternative methods are ruled as "optional" by the bill. The sponsor, who has a financial interest in the launching of new drugs, submits the evaluation of "unmet need" based on a limited population of patients. But who actually judges "unmet need"? Will this enhance antimicrobial resistance or stimulate development and use of potentially ineffective antibiotics, worsening a situation which, according to the World Health Organization (WHO) [7], already constitutes a serious threat to global health?

Regulation for medical devices and equipment is more recent than for pharmaceuticals, and novel high-risk devices (those that support or sustain human life or present potential unreasonable risk to patients) might be approved with much more fragile evidence about their safety and efficacy [1,4]. There is evidence that most devices have been evaluated by means of just a few pivotal studies that involve a small number of patients who are followed-up for short periods of time. Between 2010 and 2011, 28 high-risk therapeutic devices were approved by the FDA through the Premarket Approval Pathway. Only 82 (28.7%) of 286 clinical studies involved pivotal premarket studies, i.e. studies that served as the basis of FDA approval. Over 43% of these studies did not use any comparator and enrolled a median number of patients of 241. The median duration of primary effectiveness end point follow-up was 3 months [8].

Additionally, instead of proving to the FDA that technical changes in design or materials may result in a lack of efficacy or safety, the act enables third parties to assess developments for already marketed medical devices, and manufacturers will pay for this FDA-accredited quality assessment. The assessment will include a review the manufacturers' protocols to evaluate if the company must necessarily go to the FDA for approval [2].

The norm encourages the FDA to intensify use of other types of outcomes. Reinforcing the acceptance of intermediate or surrogate outcomes may expedite analysis. However, adoption of alternative end-points does not always predict acceptable health results for the patient. Between 2005 and 2012, approximately 45% of FDA drug assessments already considered exclusively surrogate and intermediate outcomes for novel drugs [5].

Moreover, there have been significant changes with regard to ethical procedures. Practices that were previously frowned upon, such as physicians receiving "gifts", are now acceptable if these gifts come in the form of tuition and speaking fees. There is also no obligation to disclose such gifts. Informed consent has changed, too. If only "minimal risk" is involved, this consent need not be pursued. Information and perception gaps exist between those that judge the level of risk in a trial of a new drug and those that are submitted to it [1].

In making the case for the act, there has been an acknowledgement that the current regulatory framework for the introduction of scientific breakthroughs is inadequate and that the new legislation might actually produce long-term improvements in the way in which healthcare gains are translated into benefits for patients and users [3].

While this prolific discussion ensues in the international literature, the repercussions – or perhaps translational "flow" of this new wave of thought – have already been felt in Brazil since 2011. New legislation has changed some aspects of the regulatory framework in Brazil. A federal law [9] and a federal decree [10] have defined the way in which health technologies are incorporated into the public health system. The Committee for Incorporation of Health Technologies (CONITEC) of the Brazilian Ministry of Health has a maximum period of 180 days (which can be extended for 90 days) for the evaluation of candidate technologies to be adopted and financed by the Brazilian Health System. Once the decision is made, a clinical protocol or therapeutic guideline must be produced and the technology made available in a further 180 days. These norms warranted the incorporation of medicines that later presented serious adverse effects such as telaprevir and boceprevir.

In 2013, a new decree [11] considerably shortened the market approval time to 3 months, for all medicine categories. In the wake of the 21st Century Cures Act, the Brazilian Congress is examining a bill [12] that proposes new and dangerous flexibilities for clinical research. They may compromise the health protection of subjects for the following reasons: firstly, since sponsors become exempt from providing health care to participants and may appoint auditors for the clinical trials; secondly, because the use of placebos as comparators has become acceptable.

The bill also has ethical implications. In "emergency" situations trial sponsors would not seek a priori informed consent. In addition, there is no treatment access guarantee for those who attain positive health results from the trial. Lastly, healthy participants in Phase I trials may now receive payment for participation, something which the Brazilian ethical guidelines have always been staunchly against.

What does all this really mean? A step into the future or an enormous pitfall for patient safety? It is difficult not to side with the negative aspects of these changes. In Brazil, as in many other developing countries, the Brazilian Ministry of Health should take steps to invite the carrying out of clinical trials, provided that they are conducted ethically and supported by an ethical assessment of need. Brazil has a tradition in implementing ethical guidelines (since 1996) and has taken steps to ensure that clinical research is carried out in an ethical environment. The ongoing regulatory changes may speed up licensing and assessment of health technologies, without proportional improvements for health. Coupled with lax ethical guidelines, this "recipe" may result in augmented risks for patients and users.

The butterfly is fluttering its wings.

Contributors

C. G. S. Osorio-de-Castro was responsible for developing the study, interpreting and analyzing information drawn from the literature, writing up the text, critical revision of the article and approval of the final version. R. Caetano and V. L. E. Pepe participated in the development and writing of the text, interpretation and analysis of the information, critical revision and approval of the final version.

1. 21st Century Cures Act, HR 6, 114th Cong, 1st Sess (2015). https://www.congress.gov/114/bills/hr6/BILLS-114hr6rfs.xml (accessed on 27/Aug/2015).
2. Zuckerman D. Understanding the controversies over a groundbreaking new health care law. Milbank Q 2015; 10 Aug. http://www.milbank.org/the-milbank-quarterly/the-op-eds/understanding the-controversies-over-a-groundbreaking-new-health-care-law.
3. Brindley DA, Arshad Z, Luo D, Dopson S, Hollander G, Frost S, et al. 21(st) Century Cures Act: an act of cure or diagnosis? Rejuvenation Res 2015; 18:295-8.
4. Avorn J, Kesselheim AS. The 21st Century Cures Act: will it take us back in time? N Engl J Med 2015; 372:2473-5.
5. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutics, 2005-2012. JAMA 2014; 311:368-77.
6. Centre for Innovation and Regulatory Science. New drug approvals in ICH countries 2005 – 2014. Focus on facilitated regulatory pathways and orphan designations. London: Centre for Innovation in Regulatory Science; 2015. (R&D Briefing, 57).
7. World Health Organization. Antimicrobial resistance global report on surveillance. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1 (accessed on 30/Aug/2015).
8. Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011. JAMA 2015; 314:604-12.
9. Brasil. Lei nº 12.401, de 28 de abril de 2011. Diário Oficial da União 2011; 29 abr.
10. Brasil. Decreto nº 7.646, de 21 de dezembro de 2011. Diário Oficial da União 2011; 22 dez.
11. Brasil. Decreto nº 8.077, de 14 de agosto de 2013. Diário Oficial da União 2013; 15 ago.
12. Brasil. Projeto de Lei do Senado – PLS 200/2015, de 7 de abril de 2015. http://www12.senado.gov.br/ecidadania/visualizacaomateria?id=120560 (accessed on 31/Aug/2015).

Submitted on 01/Sep/2015
Approved on 09/Sep/2015