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FRAMING AN INTEGRATED AND ADAPTIVE REGULATORY OVERHAUL OF MEDICAL TECHNOLOGIES:

A REGULATORY SCIENCE AND HEALTH ECONOMICS PERSPECTIVE

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1. Introduction

Why regulate? There are two salient characteristics in health that boost the need for regulation: informational inadequacies and a social rationale. In health care, *informational inadequacies* are pervasive. Considering health care mostly as a credence good summarises the whole concern. Patients are never sure about the extent of the goods they actually need. Therefore, "sellers"-physicians act as experts determining the patients' requirements in a situation where an expert knows more about the type of goods or service the consumer needs than the consumer himself. The expert seller is able to identify the quality that fits a customer's need best by performing a diagnosis. This information asymmetry between buyers and sellers obviously creates strong incentives for sellers to misrepresent the appropriate services (Dulleck and Kerschbamer, 2006). On top of that, uncertainty in medicine decision making has unique implications on outcomes.

Potential opportunism from exploiting such informational advantages may distort value created, or its appropriation. As far as such unbalances are well documented in presence of conflicts of interest (Moore *et al*., 2005), some regulation is needed to avoid the worst consequences in health.

Informational asymmetries and incompleteness are an intrinsic feature in health markets. This is a fact beyond considering a market failure that distorts competition, and that regulation could restore the situation to the equilibrium point. Regulation is necessary to mitigate the impact of informational inadequacies, however it may be not sufficient.

As far as western societies have evolved and introduced universal health coverage, we can argue that there is a *social rationale for regulation* beyond a strict consideration of informational inadequacies. Such rationale may stem from understanding equity of access to health services as a social value, and even health care as a citizen's right. Mandatory coverage is the regulatory answer to informational insurance market failures, but regulator may want to go further by protecting patient´s access to services (reducing or prioritising waiting lists, or guaranteeing continuity or availability of service).

Beyond the two salient rationales for health regulation, there are additional issues that in some way or another may justify intervention: *externalities, anti-competitive behavior, public goods and moral hazard, planning, rationalization and coordination*. For example, the case for mandatory vaccinations raises from the societal concern over negative externalities produced from unvaccinated individuals. As far as health care is covered under insurance, moral hazard may distort appropriate utilization and regulator should take into account measures to mitigate its impact. Or take the case for access to health services in rural areas that may require plannning and an intervention on underserved areas. Usual anti-competitive behaviours, dominant position abuse or predatory princing, also have to be under scrutiny in the health care. The guarantee of quality standards especially when the number of procedures performed is low may require rationalization and coordination, e.g. transplants and occasional surgeries. Then concentration of such procedures will take advantage of scale, learning and experience.

A government that is assumed to be acting on pursuit of the public interest should have an active role in protecting citizenship from market failures and defend its rights and social values. Of course, health lies at the top of citizen´s preferences, and this is the reason why appropriate (good) regulation is specially required.

There are five main theories that offer potential explanatory frameworks regarding regulation: public interest, capture, special interest, money for nothing, and bootleggers and Baptists (Baldwin, 2012). The initial perspective is the public interest one, no specific scholar has created it. From this view, politicians would "automatically" serve public general preferences, rather the interests for particular groups. Though politicians are human, and this may drive to potential errors, this would be the exception, not the rule. Regulatory capture theory considers that politicians and regulators face an information and agency problem. From this view, the definition of public interest is unconcrete, and requires advice and recommendations from experts on how to address the issues. Such advice is formalized under the "rent-seeking" behaviour, where finally the politician decides on certain approach that favours one part over another. However, capture theory is not able to predict which part will prevail in this struggle. This is the reason for proposing the special interest group or economic theory of regulation. We could imagine that a proposed legislation is auctioned off to the highest bidder. Understanding which parties have the most to win or loose within the regulation allows to understand the potential outcomes. The costs of organizing the interest groups and the process are compared to the potential benefit of the political favors. There are also variants of special interest group theory, regulation would be adopted in the face of concentrated industry opposition in a setting with diffused interests. Policy entrepreneurs are able then to succeed in building coalitions to challenge dominant interests. In the extreme, coalitions of opposing interests can agree on a common rule, and when this happens they will be more successful than one-sided groups. It focuses on specific types of interest coalitions in order to predict their success.

The explanation of regulatory activities may lie beyond the exogenous factors, i.e. theories detailed above, public interest and group interest perspectives. We can take into consideration institutional factors and ideas and culture that may shape regulation. For example, the "deregulation" idea has had an enormous impact on many governments and activities, though its costs and benefits were not always assessed.

From a different perspective, behavioral economics has had a recent impact on regulatory activities. For example, the contributions by Cass Sunstein are especially relevant in this respect. He has proposed the "empirically informed regulatory approach" (Sunstein, 2011). Taking into account our cognitive constraints and distortions, our departures from rational decision making and behaviour, this approach proposes a more transparent system that is grounded in regulatory impact analysis, as the basis for regulatory decision making. It tries to help the regulatory development process; while no prediction of whose interests would win or loose, it only provides an accurate estimates and public information about costs and benefits.

In this paper we make a first attempt to structure the cornerstones of an integrated and adaptive regulatory overhaul of drugs, medical devices, diagnostic tests and surgical innovations based on their current regulatory flaws and commonalities, the principles of regulatory science, health economics, and the adaptive pathways initiative.

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2. What is *good* regulation of medical technologies?

Several contentious approaches have been developed to set up criteria intended to ascertain what *good* regulation is. No set of unequivocal criteria and benchmarks has been officially set down to assess the *goodness* of regulation of medical technologies. Inconsistent attempts can be found both among different countries and individual programmes at country level (Baldwin *et al*., 2012).

Having perused them, and assuming that no single set of criteria can be used to fully determine what *good* regulation is, we use hereby a parsimonious measuring rod consisting of an aggregation of six criteria that are intertwined commonalities of these approaches at different levels of regulation. There is no pursuit of comprehensiveness, but simply an attempt to ascertain the quality of current regulation of medical technologies by way of analyzing how it pans out after applying these criteria.

First, *appropriate legislation*. From an international outlook, regulation of drugs —both small molecules and biologics— is subject to a series of laws and rules, and their regulatory problems mainly stem from five sources: 1) the lack of clear mandates spurring and channeling innovation towards added-value, relative efficacy and safety and dissuading the pharmaceutical industry from *me too* R&D; 2) disparities between both regulatory approval and reimbursement criteria andmandates and evidentiary standards for new technologies; 3) a substantial leeway for improving methodological assessment of regulatory hurdles (efficacy and safety) before approval by increasing strictness of the appraisals; 4) the foresight of a slow implementation of adaptive pathways; and 5) sustained tolerance of improper strategies such as evergreening (including reverse payment (pay-for-delay), hard switching, defensive patenting), off label prescription, overprescription, and disease mongering (Eichler *et al.,* 2010; Eichler *et al*., 2013; Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; Eichler *et al*., 2015).

Despite regulatory policies of new devices have been ruled and overhauled, in the US their particular regulatory problems are largely due to weak law enforcement of evidentiary standards (some type III devices being approved without the evidence level required for them via the 501k scheme instead of the PMA program), and in Europe, inter alia, to inappropriate legislation and weak enforcement. Regulatory overhauls aimed at reducing these deficiencies have been carried out, but in a piecemeal fashion, consisting of patchy changes that do not impinge on their systemic and structural root causes (Cohen *et al*., 2011; McCulloch, 2012; Plum *et al*., 2009; Institute of Medicine, 2010; Institute of Medicine, 2010; Institute of Medicine, 2012; Kramer *et al*., 2012; Curfman *et al*., 2011; Campillo-Artero, 2013; Fox *et al*., 2014; Sorenson *et al*., 2014; The Commission of European Communities, 2012; Wilmshurst, 2011; US Government Accountability Office, 2011; European Commission, 2012).

In other cases innapropriate legislation is due to long delay in final ruling, such as the case of biosimilars in the US: unlike their European legislation, which came into force in 2005, the Biologics Price Competition and Innovation Act (it saught to do for biologics what the Hatch-Waxman Act did for small-molecules) was enacted in 2009-2010, but their abbreviated licensure pathway still remains incomplete (Miller *et al*., 2015; Falit *et al*., 2015; Megerlin *et al*., 2013; Brickerhoff *et al*., 2015).

As far as the regulation of diagnostic tests is concerned, legislation is insufficient and ambigous worldwide (as shown, for instance, by the mounting challenge posed by the increase in biomarkers and direct-to-consumer genetic tests lacking specific and up-to date regulatory ruling). Likewise, despite research and evaluation methods and mainframes being available for regulating surgical innovations (such as the *IDEAL* model), there are no policies for their appraisal and licensing based on quality scientific standards as those most developed for drugs (Lord *et al*., 2009; Lijmer *et al*., 2009; Annes *et al*., 2011; Lumbreras *et al*., 2009; Institute of Medicine, 2012; Lumbreras *et al*., 2008; Ransohoff, 2007; Bossuyt *et al*., 2009; Trikalinos *et al*., 2009; Qaseem *et al*., 2012; Beckman *et al*., 2011; Sistare *et al*., 2010; Hutson, 2010; Howard *et al*., 2011; Towse *et al*., 2013; Towse *et al*., 2013; Garau *et al*., 2012; McCulloch *et al*., 2009; Ergina *et al*., 2009).

The picture depicted here gives free rein to both loose interpretation of mandates and directives and overly discretionary decisions and clinical use. It also paves the way mostly to type I regulatory errors given the pressure of current incentives towards new technologies reaching the market. Weak law enforcement has long contributed to the maintenance of *status quo* in this regard (Eichler *et al*., 2013; Bauer *et al*., 2014).

Second, with respect to the *appropriatenes of regulatory procedures* for these four types of medical technologies, by and large they are not either publicly accesible in the EU and the

participation of all stakeholders in their assessment, licensing and postmarket surveillance is meager or nonexistent. The absence of specifc regulatory rules for tests and surgery worldwide stands out as another serious flaw, excluding some few countries such as Australia and the UK that have already established public regulatory bodies and passed regulations for their licensing. Further, for all technologies, there is no harmonization either between regulatory approval, reimbursement processes or evidenciary standards, and the binary, all-or-nothing approach for licensing does not fit current regulatory needs (Mestre-Ferrandiz *et al*., 2014; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; McCulloch *et al*., 2009; Ergina *et al*., 2009).

Third, *technical expertise* of regulators is difficult to ascertain. However, long-standing problems, such as the approval of a number of these four types of technologies based on repeatedly proved low quality scientific evidence supporting their efficacy and safety, and frequent type I and II regulatory errors, at least cast doubts as to the appropriate level of expertise being guaranteed on a regular basis (Eichler *et al*., 2013).

Fourth, lack of *accountability and transparency* of procedures pervades the regulation of medical technologies as has been persistently reportedwith regard to clinical trials of drugs and studies of medical devices. The reluctancy to make publicly accessible most of the information of clinical trials along with the opacity of the approval processess of medical devices provides stark examples of it (Campillo-Artero, 2014).

Fifth, the lack of harmonization of regulatory approval and reimbursement criteria leads to unnecesary externalities such as duplication of efforts, delays in approval, information gaps for regulators, payers and manufacturers, and lack of communication among them. Sixth, on the basis of the resources devoted to regulation, the reported morbidity and mortality associated with type I and II errors, and the magnitude of their opportunity costs, from both the productive and allocative standpoints, there is a considerable margin to make headway towards improving the *efficiency* of the whole regulatory process of medical technologies worldwide. The application of these criteria leads to concluding that there is an impending need to foster adaptive approval (Eichler *et al*., 2013; Mestre-Ferrandiz *et al*., 2014).

Policy choices and regulatory decisions involve trade-offs among these criteria. Their assessment should rather be limited to each particular regulatory system since the strong influence of geographical determinants —including distinct legislations—minimizes the external validity of the analyses. These difficulties notwithstanding, a number of highly significant projects are underway to improve what could become a paradigmatic case in point.

3. Regulatory strategies

As far as regulation serves to protect public interest, at least this is the intention, strategies to use depend upon the specific issues it that has to address. In health, disseminating information is a crucial activity in order to protect consumers from risks. Thes estrategies start in health in all policies, i.e. food security.

The basis of regulation is recognised usually by command and control activities, the definition of standards and its enforcement. However, rules have immediate effect, but at the same time have weakness and sometimes maybe difficult to comply. Then, regulation by incentives takes its place. Trying to modify behavior according to public interest may have effect in certain cases. For example, tax regulations are able to have impact in consumption and market behavior. The extent of its impact depends upon institutional conditions and specific issues. In pharmaceuticals, incentives for R&D stem from patent systems that confer protected rights, a temporal monopoly.

Some areas of healthcare may demand that regulation finally implies to act directly, to develop a provision activity by government. For example, the supply of organs needs a unified and highly controlled body that most of the countries organize into a public organization. However, when the level of control is less strict, contracting out for particular ends may allow the goals of regulation. Let's think for example on accreditation of quality activities. Thus, different strategies appear available for regulation, depending upon the issues, its strenghts and weaknesses according to the goals and outcomes implications.

4. Regulatory failure

Regulation fails when it does not meet criteria and benchmarks of *good* regulation as those listed before. Avoidable adverse events associated with type I errors, inconsistencies in standards and requirements enacted by regulatory agencies, shortage of information as to the efficacy and safety of an array of approved technologies, conflict of interests, and capture portray some of the failures affecting the regulation of medical technologies worldwide. Some indisputable examples of these failures are the considerable amount of drugs withdrawn from the market and the increase in recall rates of medical devices owing to safety reasons (Balwin *et al*., 2012; Eichler *et al*., 2013).

When it comes to *appropriate legislation* and the choice of *regulatory tools,* some examples of failures of paramount importance are the lack or inappropriateness of mandates and directives intended to spur the innovation of small molecules with real relative efficacy and safety and that do not deter from "me-too" R&D; those that may stifle competition with follow-on biologics and instead incentivize only incremental improvements such us "biobetters" or "biosuperiors"; the uncertainty associated with the effectiveness to expedite approval ofthe*biosimilar* and *interchangeable* designations for follow-on biologics included in the Biologics Price Competition and Innovation Act; the maintenance in Europe of a fragmented, privatized and opaque regulation of devices by means of *Notified Bodies* in lieu of a central, independent, strict transparent and public regulator; the acknowledgement of the US Supreme Court that the prevailing notion of *substantial equivalence* for devices does not assure either their safety or efficacy, as well as the low compliance with the approval of type III devices via mechanisms intended for those of medium and low-risk; the absence of requirements in place for technical validity, clinical validity and clinical utility as the first barrier for the approval of diagnostic tests; and the approval of genetic tests with disregard of these three criteria along with recreational genetics, and the unregulated surgical innovations (Eichler *et al*., 2010; Eichler *et al*., 2013; Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Institute of Medicine, 2010; Institute of Medicine, 2010, Institute of Medicine, 2012; Campillo-Artero, 2013; Miller *et al*., 2015; Falit *et al*., 2015; Magerlin *et al*., 2013; Brinkerhoff *et al*., 2015; Annes *et al*., 2011).

Similarly, as regulation stands, *inappropriate regulatory procedures and procesess* are salient failures. For instance, as far as clinical trials are concerned, low samples sizes, short duration, incorrect comparators, use of inadequate surrogate and composite variables are worth mentioning flaws. Regarding devices, the variability of requirements established in different countries, the poor performance of some *Notified Bodies*, and the absence of a central record of applications are noticeable. The approval of many diagnostic tests only showing clinical validity, and often endorsed by studies containing serious methodological flaws stand out as a worrisome failure. Some others have been noted before in relation to surgical innovations (Campillo-Artero, 2014; Institute of Medicine, 2010; Institute of Medicine, 2012; Kramer *et al*., 2012; Sorenson *et al*., 2014; The Commission of the European Communities, 2012; Wilmhurst, 2011; US Government Accountability Office, 2011; European Commission, 2012; Hutson, 2010; Howard *et al*., 2011; Towse *et al*., 2013; Towse *et al*., 2013; Garau *et al*., 2012; McCulloch *et al*., 2009; Ergina *et al*., 2009).

Both inadequate mandates such as those of medical devices in Europe and their weak enforcement translate failures as well. A case in point is creative compliance (side-stepping regulations without breaking their formal tems: misclassification of type III and II devices, the obstinate refusal to release clinical trial data by unduly calling for data protection). All these regulatory flaws lead to the loss of reputation of regulatory officials and institutions, which can be considered a downright additional flaw (Baldwin *et al*., 2012).

When considering solutions to regulatory failures, thosethat exclusively hinge on one single measure are doomed to failure. One of the strenghs of the Adaptive pathways initiative is that it embraces an array of measures that impinge on all these failures (Eichler *et al*., 2012; Eichler *et al*., 2015).

5. Regulating risks

The major goals of regulation of medical technologies is minimizing health risks pursuant to the assessment of the safety reports that medical technology producers hand in to the regulatory authorities (Baldwin *et al*., 2012).

On the regulator side, the risks that medical innovations pose to health should be precisely identified and accurately scored. Here lies the first deficiency as to the regulation of risks. As for new drugs, although their risks and benefits must be ascertained during the approval process, quantitative risk–benefit assessment is not typically performed, nor is it presented in a consistent framework when it is used. Therefore, available quantitative risk-benefit assessment methods should be used to help lessen concern over subjective assessments and to guide regulatory authorities towards more objective, safe and transparent decision-making. In addition, several quality assurance problems of drugs included in clinical trials have been reported in both developing and eastern countries (those with no, little or too much active ingredient, with inadequate bioavalability, those that are not bioequivalent) (Guo *et al*., 2010; Euopean Medicines gency, 2001; Newton *et al*., 2015).

As for devices, the series of reported safety problems largely stem from two root causes. First, the well-known quality deficiencies affecting the studies assessing both their efficacy and safety. And second, in the US the abovementioned risk misclassification of type III and II devices, which is trying to capture the risks of new complex devices. In the EU, a third cause is the proved poor and sometimes fraudulent performance of some *Notified Bodies* in connection to the assessment and reporting of risks. Diagnostic tests, biomarkers and surgical innovations virtually lack an assessment of risks undertood as an outright second hurdle as that for drugs and devices (Cohen *et al*., 2011; McCulloch, 2012; Plum *et al*., 2009; Institute of Medicine, 2010; Institute of Medicine, 2010; Institute of Medicine, 2012; Kramer *et al*., 2012; Curfman *et al*., 2011; Campillo-Artero, 2013; Fox *et al*., 2014; Sorenson *et al*., 2014; The Commission of European Communities, 2012; Wilmshurst, 2011; US Government Accountability Office, 2011; European Commission, 2012).

Regulation still falls short of a sound, evidence-based, stringent and conclusive approach for identifying and anticipating risks, as well as for stratifying the assessment —specially of tests and surgical innovations— according to the risks they pose to life. High-impact-low-probability, high-probability-low-impact, discrete, and pervasive risks must be clearly identified and adequately managed (Baldwin *et al*., 2012).

A resilient regulatory attitude prevails over an anticipatory approach, hence dodging the precautionary principle. The shortages of postmarket surveillance, largely owing to underdetection and underreporting of adverse events, should be added to this tally of deficiencies of the regulation of risks (Baldwin *et al*., 2012).

Additionally, risk regulation consumes resources. Given the safety problems of established regulatory regimes attributable to the abovementioned causes, the opportunity costs of leaving risk regulation as it stands likely exceed those of strenghthening safety regulation.

In order to streamline the regulation of risks, several factors must be considered before putting into effect a host of regulatory reforms. Responsiveness of the producers of medical technologies and their disposition to comply with new requirements should be anticipated. A reasonable margin of discretionary decision making ought to be foreseen, and local political, institutional, organizational and cultural main features and constraints forestalled. When regulatory power and responsiblities are shared among several institutions coordination must be warranted. If more than one intervention is deployed, it should be secured that they do not undercut each other, as well as their timeliness. Unresponsiveness to shifts in objectives, priorities or interventions, different regulatory modes or codes, and delay run counter appropriate implementation of safety improvement actions and lessens confidence of steakeholders. These are some of the challenges faced by the Adaptive Pathways initiative (Baldwin *et al*., 2012; Eichler *et al*., 2012; Eichler *et al*., 2015; The Brookings Institution, 2015; Woodcook, 2012).

Furthermore, if postmarket risk management should be a matter of public regulation or can be delegated and left for private handling is not a contentious issue anymore. A conspicuous, spear head iniciative that has just been launched by the Brookings Institution is the Medical Device Surveillance System, an all-stakeholders partnership intended ultimately to strenghthen the postmarket surveillance of medical devices on a national basis (The Brookings Institution, 2015).

The evaluation of the implementation of new regulatory actions, the achievement of objectives, the improvement in patient safety and the efficiency of the regulatory models in place should be compulsory. Since there is ample room for improvement in the regulation of risks, the information provided by rigorous evaluations is paramout in order to fulfill this goal. The strenghthening of adaptive pathways including early-access, conditional approval upon receival of new evidences, strict compliance with approved indications, control of prescription and utilization, comparative effectiveness, postmarket surveillance, adaptive prices and the adequate use of risk sharing schemes are some of the central tenets of adaptive pathways aiming at minimizing risks as well (Eichler *et al*., 2012; Eichler *et al*., 2015; Woodcook, 2012; Baird *et al*., 2014).

6. Regulatory standards, principles and benchmarks

One salient challenge faced by any attempt aimed at improving regulation of medical technologies is the overhaul of inappropriate design, process and outcome established standards, some of them arising from a long-standing deficiency: regulation does not keep pace with the dinamics of technological R&D concerning all types of medical technologies. There is an impending need to raise and harmonize evidentiary standards for both their regulatory approval and reimbursement. The prevailing binary, two-stage assessment and approval system cannot fulfill the different informational needs of regulators and payers (Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; Eichler *et al*., 2015).

All this meansthatthe requirements and assessment of information regarding absolute and relative (added, incremental) efficacy and safety of technologies should be integrated. Although comparative effectiveness studies have gained traction over the last years, they should also be further strengthened and coordinated with premarket studies (randomized controlled trials should be complemented with pragmatic trials and observational studies), thus reducing the gap between efficacy and effectiveness. Moreover, effectiveness and safety evidence provided by strong postmarket surveillanceand comparative effectiveness is needed in order to flesh out that obtained in premarket studies, help in deciding adaptive licencing and prices (Campillo-Artero, 2014; Towse *et al., 2013;* Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; *Eichler et al*., 2015 2015; Messner *et al., 2015;* Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; Eichler *et al*., 2015).

Therefore, regulatory officials must abandon their indecisive attitude and make headway towards requiring, not *urging*, the sumission of added-value evidence, perform value-based assessment, pricing and reimbursement, and definitely foster harmonization of standards and processes. To attain this last goal, four general and complementary approaches have been set forth and are currently underway in some countries: aligment of evidentiary requirements, early tripartite dialog (regulators, payers and manufacturers), parallel submission of documentation for assessment, licensing and reimbursement, and adaptive pathways, which are being piloted in the US (MIT, FDA), Europe (EMA), Canada, Japan, Singapore, and Australia, among others (Campillo-Artero, 2014; Eichler *et al.,* 2015; Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi *et al*., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; Eichler *et al*., 2015; Mestre-Ferrandiz *et al*., 2014; NICE, 2014; Mattes *et al*., 2010; Campillo-Artero, 2015; Tsoi et al., 2013; Campillo-Artero, 2014; Eichler *et al*., 2012; Eichler *et al*., 2015; European Medicines Agency, 2014; European Medicines Agency, 2014).

Further, the existence of ambiguousand confusing wording in standards and rules in

directives and mandates (i.e., "reasonable assurance," "substantially equivalent", "probable benefits", "essential requirements", "similar effectiveness", "significant innovation", "biosuperior" or "biobetter"should be definetly abandoned (Campillo-Artero, 2015; Campillo-Artero, 2014; Campillo-Artero, 2013).

It has been claimed that both the quality and the level of scientific evidence gathered and handed in within applications for approvals of medical technologies does not reach minimmum scientific standards often. Therefore, current levels and rules for quality ought to be raised specifically by considering the type of technology —that determines the nuances, the capabilities and the applicability of the methodological tools available—, the culture and experience of research and evaluation of clinicians, and the resources and incentives available. Compared to using solely one source of data for decision making, the marginal gains of combining that contained in sponsors applications, regulatory reports, assessments made by health technologies assessment, registries, horizon scans and comparative effectiveness studies are sweeping (Wilmshurst, 2011; US Government Accountability Office, 2011; European Commission, 2012; Lumbreras *et al*., 2008; Newton *et al*., 2015; Köler *et al*., 2015; Yordanov *et al*., 2015).

In addition to drugs, thorough standards are needed for the approval of diagnostics on the basis of their diagnostic added value (i.e. reduction of the time elapsed between diagnosis and treatment, improved diagnostic, predictive, prognostic, and pharmacokinetic accuracy), and incremental cost-effectiveness. Alongside the strengtheningof the scientific underpinnings of biomarker developement, their technical validity, analitical validity and clinical utility should be considered in tandem with the main criteria for their approval. Biomarkers ought to fulfill standards set forth in connection to validation and qualification before being approved as noted elswhere. Studies and reports submitted to regulatory officials for approval that dodge measures of the real influence of the technology on health outcomes should be deemed incomplete and rejected (Campillo-Artero, 2012; Lord *et al*., 2009; Lijmer *et al*., 2009; Annes *et al*., 2011; Lumbreras *et al*., 2009; Institute of Medicine, 2012; Lumbreras *et al*., 2008; Ransohoff, 2007; Bossuyt *et al*., 2009; Trikalinos *et al*., 2009; Qaseem *et al*., 2012; Beckman *et al*., 2011; Sistare *et al*., 2010).

The documented virtual absence of regulatory standards for surgical innovations calls for implemeting those that are tantamount to relative efficacy and safety in addition to the "fourth hurdle" for public coverage. In their regulation, similarly to that of diagnostic tests, a phase evaluation based on the main principles of randomized controlled trials should be deployed. Several models have been proposed for this end, such as the phase evaluation model for tests and the IDEAL model for surgical innovations. Given their current degree of development, they only need to be fleshed out and implemented while considering local implementation conditions including barriers, and taking into account that its tenets are consistent with those of the adaptive pathways (Campillo-Artero, 2014; McCulloch *et al*., 2009; Ergina *et al*., 2009).

This notwithstanding, current standards and enforcement in a number of countries still fall short of this impending need thus leaving free rein and encouraging marginally incremental, *me-too* innovations. This being the case, losses in social efficiency continue to ensue in regulatory regimes that have not adopted value-based regulatory methods and efficacy and safety standards together with adequate incentives for assesssment, licensing, pricing, reimbursement, and postmarket evaluation directed towards spurring real added-value innovation.

Moreover, principles and standards intended to contribute to ensuring undisputable evidence-based, self-improving, timely regulation, along with the participation of all stakeholders must be endorsed. Likewise, when lacking or where failing, those directed to harmonize assessment, appraisal, coverage, pricing and reimbursent standards accross countries and regions need to be reinforced. Unequivocal identification and registry standards for all four groups of technologies must be secured, as well as those aimed to guarantee their accurate and reliable classification on the basis of the risks they pose to health (Campillo-Artero, 2014).

Consistent with the adaptive pathways, setting stringent prescription and utilization standards alongside the evidence provided by postmarket surveillance and comparative effectiveness are needed to regulate the licence or withdraw from the market of technologies reaching or failing to fulfill the standards (Eichler *et al*., 2012; Eichler *et al*., 2015; Baird *et al*., 2014; Towse *et al*., 2015; Messner *et al*., 2015).

7. Regulatory enforcement

The specific regulatory objective of making laws and rules effective requires at least *appropriate* mandates and standards in force, their being adequately tailored to the main features of each medical technology, consistent with social values, efficiency and equity principles as they apply to innovation needs, and that resources and incentives aimed at making all stakeholders do what is required by law are in place and aligned. Among the diverse models that have been used to ascertain regulatory enforcement, we consider the DREAM framework (Detecting, Responding, Enforcement, Assessment, and Modification) parsimonious and useful to apply it here (Baldwin *et al*., 2012).

Pursuant to this framework, *detection* tools of compliance have failed when it comes to approval, postmarket control activities, (over)prescription and (over)overdiagnosis. Nevertheless, a substantial fraction of these tools have been devised and applied by entities and profesional outfits outside the regulatory agencies (mainly Academia and groups of clinicians belonging to profesional societies or ad hoc expert committees), to mitigate the detection shortfalls in the evaluation of compliance by official regulatory agencies both before and after technologies reach the market (Laine, 2012; Siwek *et al*., 2013; Dyer, 2013). Detection tools having enough sentitivity should be incorporated into the services portfolio of public regulation agencies and be used on a regular basis.

Regarding diagnostic tests, *detection* activities and tools are on the rise but they are not all-embracing yet as compared to those for drugs and devices. Detection actions regarding surgical innovations are intheir very earlier stages of developement and should be fostered (McCulloch *et al*., 2009; Ergina *et al*., 2009; The Brookings Institution, 2015).

Responding, the next task of enforcement, consists of developing rules and tools for detecting non-compliance, undesirable behaviour and producing compliance with mandates. Amendement and refining in responding calls for reviewing rules that are not accompanied by due sanctions or do not cover undesirable conducts of producers thus giving free rein to mischief. The available predicting tools of the levels of compliance and creative compliance of producers that will be associated with the enactment of a given ruling should be applied (Dulleck *et al*., 2006). They will be badly needed to fulfill some goals of the adaptive pathways such as the use of appropriate surrogate variables, early access, conditional approval, limited initial coverage, compulsory postmarket generation of evidence, strict prescription, adaptive approval, pricing and withdrawal (Eichler *et al*., 2012; Eichler *et al*., 2015; Woodcook, 2012; Baird *et al*., 2014; Towse *et al*., 2015; Mesner *et al*., 2015).

Regarding *enforcement,* increasing compliance with these rules and policies can largely be done by applying the most appropriate of a variety of available strategies such as command and control, deterrence, or principle-based regulation. Different combinations of the principles and values of these two extremes fill the gap in between (Baldwin *et al*., 2012).

However, strategies to transfer the risk management and responsibility to firms are not enough when we are talking about "credence goods" instead of "inspection goods" or "experience goods" (Dulleck *et al*., 2006). In the last two cases, one may infer the quality from having a look at it or trying it (if possible). In credence goods, you may not know the quality even after you have provided the service. That's why you do need a third party that regulates entry in the market and establishes surveillance activities (medical devices and drugs) (Dulleck *et al*., 2006).

Enforcement actions can be taken to prevent an act that leads or may lead to harm (preventative), in response to this act (act-based) or can be prompted by the realization of harm (harm-based). The appropriateness of each of these options rotates around the trade-offs between the costs, the resources needed, the predicted level of compliance of producers to the

standards and rules, the feasibility of each strategy, the potential harm that may ensue in the absence of enforcement, and both the benefits reaped in terms of avoided harm or inefficiencies and the costs of reversing harm when it is realized (Baldwin *et al*., 2012). The closer to the preventative actions, the higher the likelihood to maximize regulatory efficiency and patient safety.

The current EU regulatory system for devices, and both the US and the European systems for diagnostics and surgical innovations are mainly harm-based. The magnitude of avoidable adverse events reportedly associated with them underlines the impending need to shift towards a preventative approach. Concerning drugs, postmarket pharmacosurveilance should be enforced as commented before.

Additionally, a host of exemples of information asymmetry undermines the effectiveness and efficiency of all these approaches: scandals involving the abovementioned protheses, defective implantable defibrillators, the concealment of side effects of drugs in clinical trials, the increase in use of evergreeningto delay the expiration of patents known (hard switching being one of the last on which legal actions have been taken in the US) or the externalities associated with presymtomatic direct-to-consumer genetic tests available in the market with uncertain clinical validity and unproven clinical utility being on the rise. The lack of transparency of the regulatory processess carried out by *Notified Bodies* in the EU brings another cristalclear example that will not be solved as has reportedly been pointed out in light of the slight reforms and amendements underway of current regulation of devices in the EU (Campillo-Artero, 2015; Campillo-Artero, 2013; Annes *et al*., 2011). The opportunity costs of maintaining the *status quo* of these bodies maybe high.

On the basis of these and other negative spillover effects of current regulatory systems of medical technologies light-touch, pure principle-based regulation strategies are untenable. Regulators ought to consider the marginal costs of enforcement as the levels of compliance and the strictness of rules increase, and that the optimal level of enforcement gravitates towards the point where the marginal cost of enforcement equals the marginal benefits reaped in terms of avoided harm.

The *assessment* of the degree to which the goals of regulatory enforcement are being accomplished involves ascertaining both the way enforcement is carried out and the effectiveness of enforcement activities. Enough evidence has been collated as to the insufficiencies of the former (that focus on inputs and processess) and the latter (that do so on outcomes). Enforcement problems do not only stem from detection flaws but also from correct standard setting and the implementation of some of the effective and efficient enforcement strategies intended to improve compliance. As it has been shown in some official reports, in the US and the EU some of adverse events associated with defibrilators, left atrial appendage occluders, hip prosthesis, morcellators and other devices reveal reviews that are more focused on device performance than on clinical effectiveness and safety (Campillo-Artero, 2015; Campillo-Artero, 2014; Dhruva *et al*., 2009; Fraser *et al*., 2011; Messe *et al*., 2008; Congolani *et al*., 2011; Kramer *et al*., 2015; Dyer, 2014; Gerber *et al*., 2011).

When it comes to *modification*, a number of assessments have already provided a wealth of well-grounded information that suffices to bring about the changes needed to streamline the regulation of drugs and devices, and to definitely step up and forward a comprehensive pre-post approval interactive regulatory system for diagnostics and surgical innovations, that is consistent with the main principles of regulatory science and the adaptive pathways (Eichler *et al*., 2012; Eichler *et al*., 2015).

Five important enforcement examples should be noted in this regard. Similarly to Canada, german regulators will assess the extent of additional benefit of the new drugs and to fix the price based on the following classification: remarkable additional benefit; considerable additional benefit; minor additional benefit; additional benefit not quantifiable; no evidence ofadditional benefit; and less benefit than thecomparator (Gerber *et al*., 2011). Likewise, the French regulator, launched in 2013 the new Relative Therapeutic Index, also based on relative efficacy criteria and consisting of five categories, each of which will be linked to certain rules regarding price: lower (no reimbursement); similar (lower price); marginal benefit (same

price); moderate benefit (price negotiated); and major benefit (european price) (Inspection Générale des Affaires Sociales, 2013). In the same vein, the Center for Medicare and Medicaid Services has become more stringent at analyzing evidence and more skilled at assessing study quality for national coverage and reimbursement determinations. It is increasingly using coverage with evidence development policies had has, in sum, raised the evidenciary bar over the last years (Chambers *et al*., 2015). Further, the NICE´s Medical Technologies Evaluation Programme for medical devices, launched in in 2009, has so far advanced in attaining their goals (simplify access to their evaluation, speed up the process and increase the NICE´s evaluative capacity), even though it is premature to assess its impact in the final decision making concerning approval of devices (Chapman *et al*., 2014). Finally, given the need to foster socially desirable innovation in the realm of drugs, a host of scales indicating how innovative they are, have started to be applied by the FDA and Medicare (Campillo-Artero, 2015; Lanthier *et al*., 2013; Robinson, 2015).

Concerning diagnostic tests, *modification* deficiencies are twofold: adding evidenciary standards for approval to those already established (clinical utility, diagnostic added value), and enforcing them by means of available strategies and adequate incentives. In conection to drugs, WHO and ICH requirements in force for quality assurance of drugs used in clinical trials fall short of the perils of the international drug market where wanting regulatory surveillance continues to result in variations of drug quality (they have not been updated since the 1990s) (Newton *et al*., 2015).

With regard to diagnosis, prognosis, predictive and pharmacogenetic biomarkers, standards for *validation* and *qualification* ought to be definitely ruled and enforced, a specially those concerning qualification (it has to be ensured that biomarkers are linked to biological and clinical outcomes). Besides, the incentives to continue discovering and developing biomarkers and the need to focus on those for which evidence has been gathered should be balanced. Criteria for the initial selection of biomarkers have already been set up. Enforcement activities should fight shy of their assessement being based on cherry-picked data and their being prematurely deployed in routine clinical practice (Campillo-Artero, 2014; Beckman *et al*., 2011; Sistare *et al*., 2010; Howard *et al*., 2011; Towse *et al*., 2013; Towse *et al*., 2013).

Finally, consumer protection on health issues demands a strict functioning of regulatory institutions. In Europe, regulatory activites lie in a multi-level administration framework. The key elements stem from unified directives that are binding on the results to be achieved and all states have to adopt with certain discretion over methods. Most of the administrative activities are in the hands of national and regional services. The mutual recognition principle plays a key role in this structure. Officials have to rely on practices performed by other officials and this imposes obligations to all parties, but this principle is applicable in certain regulatory areas (i.e. food policy) while depending upon the legal issue there aren't common practices (i.e. genetic tests). Therefore, there is a need to reassess the implications of metal-level regulatory activities in health according to these issues and especially to focus on those that remain unmanaged or uncoordinated.

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