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Methodological tensions in risk assessment and benefit assessment: a classification

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Abstract
This article analyzes some of the methodological tensions that can be observed in the regulation of science and technology, and that often manifest themselves as controversies. We offer a three-way classification of such tensions. The latter can arise from: 1) external (non-cognitive) factors that are specific to a particular regulation; 2) external (non-cognitive) factors of wider societal importance that are *not* related to any particular regulatory process; and 3) internal (non-cognitive, as well as cognitive) factors related to the cognitive, as well as practical limitations of a particular scientific methodology in the

context of regulatory decision making. We analyze case studies of regulation of, among other, pharmaceuticals, chemical products, health claims on foods, as well as genetically modified organisms. The analysis shows that most often such methodological tensions are driven, directly or indirectly, by different stances with respect to non-cognitive factors that underlie the fundamental choices of methods and standards, and therefore the data that underpin regulatory decisions. Our paper makes clear an important feature of regulatory science: cognitive factors (like improved scientific data or accepted best practices), that in academic science facilitate the resolution of debates, in regulatory science do not suffice for achieving closure with respect to such tensions. Any attempt at closure has to deal primarily with the relevant non-cognitive factors.

Keywords: regulatory science, risk assessment, benefit assessment, non-cognitive factors, regulatory controversy

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1. Introduction

This article analyzes some of the methodological tensions that can be observed in regulatory science. Such tensions are commonly related to methodological choices, regulatory objectives, the operationalization of regulation, as well as concomitant regulatory decisions. In many cases tensions manifest themselves as debates or controversies.

The regulation of products and processes based on science and technology commonly requires the concourse of scientific data in order to be able to take regulatory decisions. The use of science for such purposes is known as regulatory science (Jasanoff 1990). Regulatory science is characterized by the application of scientific methods and standards for data generation that, however, in many cases differ from the scientific methodologies typically found in academic science (Cranor 2011; Luján and Todt 2018).

Academic science is the type of science as it is practiced commonly in universities and research centers; its primary aim is the generation of knowledge about the natural and social worlds for academic purposes, i.e., for knowledge's sake, for being able to make certain predictions, and so on. For the purposes of this text, we will term this kind of science 'knowledge-oriented science'. We have to clearly differentiate such knowledge-oriented science from regulatory science, given the differences in methods, standards and objectives between both kinds of science (Cranor 2017; Luján 2023). This applies above all to their purpose and objectives: regulatory science aims at generating scientific knowledge for a particular, well-defined purpose, that is, underpinning regulatory decisions. As a result, in regulatory science the influence on methodological choice of non-cognitive factors –as distinct from purely cognitive (epistemic) factors– has to be given particular attention (Todt and Luján 2022).

Thus, in this paper we analyze some of the methodological tensions that arise in regulatory science. We present a classification of different types of such tensions, according to the main drivers that give rise to those tensions in the first place. Our analysis indicates that tensions in regulatory science are driven by different stances with respect to the *non-cognitive* factors that underlie the fundamental choices of methods and standards, and therefore the data that underpin decisions.

Non-cognitive factors include a broad range of elements that may play a role in regulation and policy making; they range from regulatory objectives (like protection of human health and the environment) and considerations related to a regulation's practical operationalization (including efficiency) all the way to individual and collective attitudes, values and beliefs, as well as broader societal, cultural and political (for instance, ethical) issues. Purely cognitive factors, in contrast, are less important to (and may even be completely absent from) regulatory controversy; they are mostly related to contextual

issues (the question not being, for instance, the general limitations or implications of a particular scientific methodology, but rather its limitations or implications in a particular real-world context of importance to a specific regulatory process).

We argue that closure of controversy, particularly methodological controversy, in regulatory science tends to be different from closure of controversy in knowledge-oriented science. In the latter, it is the cognitive factors that typically facilitate the resolution of debates. This contrasts with regulatory science, where appeal to cognitive factors does not suffice. Rather, closure may only be achieved by dealing with the *non-cognitive* factors that underlie most regulation-related debates.

2. Tensions in Regulatory Sciences

Our objective here is to offer a classification of the various types of tensions that can be observed in regulatory science, including the areas of risk assessment and benefit assessment. Not all such tensions and related controversies are of the same type, nor driven by the same motives. Thus, we can encounter different driving forces and objectives, some internal, others external to the relevant regulatory process.

We offer a three-way classification of drivers of regulation-related methodological tensions: 1) external (non-cognitive) factors that are specific to a particular regulation (mostly the objectives of a regulation); 2) external (non-cognitive) factors of wider societal importance that are *not* related to any particular regulatory process (mostly ethical questions about, for instance, the use of animals in data generation); and 3) internal (non-cognitive, as well as cognitive) factors related to the cognitive, as well as practical limitations of a particular scientific methodology in the context of regulatory decision making.

The proposed classification is tentative and based on a limited number of case studies from several regulatory processes. It does not aspire to completeness. Rather, the objective is to show that there are a number of clearly differentiated drivers in regulatory science that lead to tensions and controversy.

3. Methodological tensions stemming from *external* (non-cognitive) factors that are *directly related* to a particular regulatory process

This category comprises tensions that for the most part are related to the objectives or aims of particular regulatory processes. The tensions and related controversies are motivated by questions like ‘What is this particular regulatory process good for? Why do we regulate this

particular product in the first place? What are the outcomes to be achieved by regulating the product or technology at issue?'

In order to analyze this type of regulatory tensions, we will resort to two case studies: 1) the regulation of health claims on foods, and 2) the regulation of genetically modified organisms (GMOs).

Our first example concerns the regulation of health claims in the European Union (EU). Health claims are statements, usually in the form of food labels, with respect to the additional health benefits (like long-term maintenance of correct blood pressure) that consumption of a particular food item confers upon its consumers (Bagchi 2019). In the EU, as in many other jurisdictions, such claims are regulated due to the added value they provide for a food item (European Parliament and Council 2006). The controversy with respect to the European regulatory process for health claims opposes two different perspectives on the very reasons for which health claims are subject to regulation in the first place, as well as two concomitant opposing strategies for regulating such claims.

On the one hand, there is the perspective adopted by the EU regulatory agency responsible for regulating health claims (the European Food Safety Authority): under this approach, the key regulatory driver is the objective of minimizing the risk of non-effective health claims reaching the market. This is meant to protect consumers from false claims. The principal EU regulatory concern is that consumers of foods with health claims might be misled into purchasing and consuming foods that do not provide the advertised health benefits (Valtueña Martínez and Siani 2017). Regulators aim at preventing consumers from relying on such ineffective food products in their quest for better health, while spending money on them. The principal problem from the regulator's perspective is to establish with a high degree of certainty the efficacy of a claim, i.e., providing certainty as to the expected health outcomes (benefits). That is because beneficial effects from consumption of certain foods commonly accrue slowly over time, may not show for decades, can be extremely subtle, and may occur only if the food in question is consumed as part of a particular food matrix (Blumberg et al. 2010). Those (and other, similar) characteristics of health effects from foods make it usually impossible for individual consumers to easily verify for themselves the existence of the advertised benefits (unlike, for instance, in the case of many pharmaceuticals whose effects are rapid and in many cases relatively easy to discern).

Interpreting the primary aim of health claim regulation as protection of consumers from false claims has a methodological implication: in order to effectively minimize regulatory approval of ineffective health claims, regulators will have to impose a very exacting level of scientific evidence. The latter generally translates into the regulatory requirement for the establishment of a causal relationship between intake of the food product in question and the desired positive health outcome. This turns clinical trials (randomized controlled trials, RCTs) into the preferred (or even mandatory) scientific methodology for generating regulation-relevant data. That is because RCTs, in principle, are the only scientific

methodology generally accepted to be able to provide data on causal relationships. Regulators (and consumers), however, pay a price in exchange for certainty: the strict evidence requirements result in an increase in false negatives, i.e., a certain percentage of actually *effective* claims being *denied* regulatory authorization due to the difficulties of reliably establishing causality.

This interpretation of health claim regulation's primary objective as being the protection of consumers from ineffective claims is challenged by a competing interpretation (Blumberg et al. 2010): the latter defends that the primary aim of health claim regulation ought to be facilitating the uptake among consumers of foods identified by health claims, with the ultimate goal of improving public health, while in the process developing a functioning market for foods with such claims (Richardson 2012). This alternative interpretation of the rationale underlying health claim regulation is based on the notion that widespread and large-scale consumption of food products identified by health claims would contribute not only to the improvement of individual consumers' health, but (through the aggregate effects) of wider public health. Therefore, facilitating consumer acceptance of foods identified by health claims is considered a fundamental (and legitimate) regulatory objective.

However, in order to reduce the number of false negatives, under this second interpretation the evidence requirements would have to be less severe than under the first interpretation; in other words, a wider spectrum of scientific methods, beside RCTs, like mechanistic or observational studies, are considered acceptable for data generation. The objective is to reduce to an acceptable level the risk of authorizing ineffective claims, without, however, requiring the establishment of causality. This is meant to provide consumers with a wide range of authorized claims on foods, even if overall the reliability of the data underlying these authorizations is somewhat lower than in the first case. Thus, under this alternative interpretation, regulators accept that a certain percentage of approved claims will turn out to be ineffective, because their primary concern is to minimize the probability of denying authorization to effective claims due to a simple lack of sufficient evidence (for instance, impossibility of establishing a causal relationship between intake and outcome).

In other words, under one interpretation, regulators aim at reducing as much as possible any false positives by applying very strict evidence requirements. In contrast, under the competing interpretation, the aim is the reduction in false negatives. Both aims are obviously incompatible with each other. This has led to a controversy in Europe about the ultimate (non-cognitive) objectives of health claim regulation (Todt and Luján 2021).

Our second example in this category is taken from the regulation of genetically modified organisms (GMOs), like –for instance– GM crops modified to be resistant to drought or pesticides. Here the controversial issue is if to regulate GMOs as a separate category of

product (or process), or alternatively if to subsume GMOs to existing, non-GMO regulation according to each type of GM-product.

The latter approach is known as substantial equivalence (Levidow and Carr 2000). This approach implies regulating a particular GM crop (or any other GMO) in exactly the same way as the equivalent, non-GM crop, applying exactly the same regulatory demands, data requirements and decision making processes to both non-GM and GM varieties (Zimny et al. 2019; Levidow and Carr 2000).

In contrast, under the approach of regulating GMOs as a separate category, the primary regulatory objective is to minimize any specific risks stemming from the process of genetic modification itself. The main concern is that the very technology of genetically altering agricultural products, foods, animals, bacteria, etc. might lead to changes in those organisms, as well as their behavior that might turn out to be harmful to humans or the environment. To minimize any such risks, under this approach *all* genetically modified plants and animals are subject to specific GMO regulation, simply for the fact of having been genetically modified. This is the type of regulation that has been adopted, for instance, by the EU (European Parliament and Council 2001). This approach has certain methodological implications. GM products are tested for specific risks for which their non-GM counterparts would not be tested (as in, e.g., establishing the effects of GM crops on nearby insect populations, or studying the interaction of GM plants with soil bacteria). Furthermore, particular scientific methods and regulatory procedures are applied to GM products that do not apply to non-GM products. As an example, GM crops are subject to systematic post-marketing monitoring. In addition, regulatory authorizations are provisional, instead of permanent, requiring regular renewal on the basis of the available data.

Under the alternative substantial equivalence approach (as adopted, for instance, in the U.S.), the objective of regulation is to minimize risks that are typically associated with the particular organism in question, e.g., its toxicity, but with independence of its way of production, GM or non-GM. In principle any GM varieties of existing, well-known and well-studied organisms (for instance, GM tomatoes) are considered substantially equivalent. They are regulated exactly like the equivalent non-GM varieties (non-GM tomatoes). Any possible risks identified in a GM variety would be expected to be the same as the ones associated with the respective non-GM variety. Specific regulation is applied only in certain cases (like GM virus) when substantial equivalence cannot be established.

Due to the tension between the two alternative regulatory objectives and scopes, a long-running controversy has developed about what the objective of GM regulation ought to be, either preventing risks that are specific to the technology of genetic modification itself, or alternatively, facilitating the development of GMOs by treating them (and any associated risks) in the same way as the equivalent non-GM organisms (Hilbeck et al. 2020; Zimny and Eriksson 2020). The tension between the two approaches extends to more recent

developments, including technologies like the editing (rather than modification) of plant genomes (for instance, CrispR) (Turnbull et al. 2021).

In sum, in both examples we observe tensions, as well as concomitant controversies, which are related to the *objectives* of a particular regulatory process, with counterpoised interpretations that have direct methodological implications for the process of generating the data that underpin regulatory decisions.

4. Methodological tensions stemming from *external* (non-cognitive) factors of wider societal significance, but *not directly* related to any particular regulatory process

The tensions in this category concern factors that are of wider societal importance but that, at least in principle, are unrelated to specific regulatory processes, or even to regulation in general. Many of these tension have their origin in issues that have an ethical component.

Our first case study in this category is the current argument against the use of *in vivo* (i.e., animal) studies for regulation-related data generation. This is a controversy that involves the questioning of the regulatory use of a particular prevailing scientific methodology on general ethical grounds. The proposed solution is the substitution of the criticized method with an alternative.

This controversy focuses on the use of animals in generating data in regulatory areas like food risk assessment or chemicals regulation (Ram, Gadaleta, and Allen 2022). The fundamental issue is if, from an ethical point of view, it is considered acceptable to use animals in data generation in risk assessment with the aim of protecting human health and the environment. The related methodological argument is that the long-standing use of animals in *in vivo* trials (for instance, in toxicology) ought to be phased out and replaced by other scientific methodologies that do not rely on animals. These alternative methods are mostly newly-developed computational (*in silico*) methodologies that are collectively known as New Approach Methodologies (NAMs) (Westmoreland et al. 2022; Krewski et al. 2020; NRC 2007).

The authors (for instance: Fentem et al. 2021) who argue against animal studies point out that nowadays NAMs and similar methodologies can be considered sufficiently mature to justify their systematic use in regulation, as long as regulators understand (and accept) that the generated data have to be processed and analyzed in fundamentally different ways (as compared to *in vivo* data) in order to be useful to regulatory decisions. This implies, among other, the widespread use in data processing of Weight-of-the-Evidence (WOE) methods (which are able to process varying data from manifold sources), due to the multiplicity of data generated by NAMs, with varying degrees of error and reliability. The authors argue that regulatory authorities, even within the existing legal and regulatory frameworks, ought to systematically promote the use of NAMs by facilitating, or even

requiring their use in regulation-relevant data generation. The same argument, furthermore, points to the experience gained in the last few years that tends to show that NAMs are in many cases able to produce data of sufficient quality and reliability for regulatory decision making (Westmoreland et al. 2022).

In current practice, however, most regulatory agencies, particularly in the EU, do not incentivize the use of such new methodologies, show inconsistent policy implementation regarding NAMs, and continue to explicitly require *in vivo* studies even in the case of relatively new regulations like those related to novel foods (Boer and Bast 2018). Regulators thus tend to favor traditional, animal-based methods because of their doubts concerning reliability and equivalence of NAM data, as well as lack of practical experience (Boer 2019).

Our second case study in this category points to a slightly different type of methodological controversy that questions the way a particular scientific methodology is applied in regulation, while arguing for changes or modifications, without however rejecting this methodology's role in regulation-relevant data generation. A case in point is the argument for trying to account for (and if possible, correct) bias in industry-sponsored data generation in pharmaceutical research.

As an example for this type of controversy, we will refer to Solomon's (2020) critique of industry sponsoring of pharmaceutical RCTs. The author argues that the demonstrated bias commonly present in data from pharmaceutical trials that in one way or another have been sponsored by the pharmaceutical industry, constitutes a serious problem due to the high percentage (around 50%) of such research that receives financial support from industry. Such trials with 'industry bias' are more likely to produce data backing the efficacy of a drug or medical treatment than similar trials conducted by industry-independent researchers. The presence of industry bias is mostly unrelated to the quality of the individual RCTs, as even high-quality industry-sponsored trials tend to produce outcomes more favorable to industry (Solomon 2020). Given the perceived lack of effectiveness of past remedies to counteract industry bias (such as disclosure or commonly agreed-upon RCT quality standards), the author proposes the introduction of a correction factor which would be applied to the results of *all* industry sponsored clinical trials. As far as our argument here is concerned, the relevant point is that Solomon (2020) does *not* question the use of RCTs in pharmaceuticals regulation; rather, what she argues for is a methodological adjustment in order to improve quality, namely, trying to correct industry bias by way of a (relatively straightforward) modification in the scientific methodology used for data generation.

Both of our case studies concern tensions that flow from general social debates with ethical import. The first case is related to the ethical argument about minimizing, as far as reasonably feasible, the use of animals in scientific research. The second case is related to conflicts of interest in research. In this latter case, the particular regulation-related ethical

matter is if it can be considered acceptable, and to what degree, that a social actor like industry sponsors research related to products in whose regulatory authorization and subsequent commercialization this actor has a primary interest.

In both of the case studies we have discussed, the regulatory tensions and concomitant controversies are directly related to general societal and ethical debates about what kinds of 'non-cognitive objectives' our society can or should aspire to. It is evident that these debates (use of animals in data generation, industry influence on research) are in principle independent of regulation, but may exert direct influence on methodological choices in particular regulatory processes.

5. Methodological tensions stemming from *internal* factors related to the (cognitive as well as non-cognitive) limitations of particular scientific methodologies in the specific context of regulatory science

The tensions in this category touch upon issues *internal* to scientific methodologies, as applied to data generation. Most of these issues concern certain cognitive, as well as non-cognitive limitations of such methodologies that take on relevance only in the specific context of their *real-world use* for underpinning regulatory decisions (Cartwright and Hardie 2012).

Here we will discuss two case studies: 1) the methodological limitations of randomized controlled trials that lead authors to argue for supplementing RCT data under certain circumstances with other types of data, or to warn researchers to be aware of those limitations because in certain cases (as in nutrition RCTs) they may restrict this method's usefulness; 2) the practical limitations of standard scientific methods in a regulatory environment (mostly due to their significant resource requirements), which from a purely practical (operational) point of view might make them largely unsuitable for use in most regulatory processes that need to produce large numbers of decisions in a timely fashion.

The first case study is an example of controversy about how to *improve, without substitution, existing scientific methods* that are relevant in the regulatory context. In particular, this comprises debates about the significance of certain methodological limitations of RCTs (clinical trials) under the particular real-world demands of regulatory science, i.e., the use of data to underpin decisions with import for health and the environment (LaCaze and Osimani 2020; Vandenbroucke 2008; Osimani 2014). A related line of critique that has led to debate concerns drug *safety* assessment. Here the principal argument is that statistical evidence may not suffice to arrive at valid regulatory decisions, and that other evidence may need to be taken into account, too (LaCaze and Winckel 2020).

These kinds of tensions are related to more or less 'practical' concerns, and refer to situations that might occur in regulation with a certain (albeit low) frequency. They can,

however, also have a more pronounced ‘philosophical’ import, in that they may also concern hypothetical or extremely unlikely situations and contexts. The point that matters is that the authors we have mentioned do not offer a fundamental critique of the method itself. They do not propose to supplant clinical trials and statistical knowledge with (data from) other types of methods; rather, they do accept RCTs as the standard method for pharmaceutical efficacy assessment (LaCaze and Winckel 2020; Osimani 2014). Their general objective is to point to possible improvements in the generation of regulation-relevant data in particular contexts. Improvements could result from, for instance, modifications to the procedures underpinning clinical trials, or –in some cases– the generation of complementary (for instance, mechanistic) information. More generally, authors exhort pharmaceutical scientists to not oversell the benefits of clinical trials (LaCaze and Winckel 2020).

Another tightly related argument (Rocca, Anjum, and Mumford 2020; Vandenbroucke 2008) concerns the opposition of ‘knowing-that’ and ‘knowing-how’. This is the well-rehearsed issue of RCTs providing data on statistical relationships only, but not answering the ‘why?’ questions. It may thus be necessary to complement, at least under certain circumstances, statistical knowledge from clinical trials with mechanistic knowledge (Luján and Todt 2021). The latter makes reference to knowledge that would let us understand the biochemical pathways by which an outcome is produced. For instance, there are cases in which it might not suffice to have established that a statistical relationship between intake (of a drug or a food item) and a particular outcome (endpoint) holds. One such situation might be the treatment of one particular (single) patient, as opposed to the treatment of large numbers of patients. There are also certain contexts in which mechanistic knowledge might be of importance, for instance when it is unclear if the real-world environment can be successfully mimicked by the controlled environment of a clinical trial, be it for drugs or foods (Richardson 2012). In the case of pharmaceuticals, unforeseen effects of drugs can point to problems with reproducing real-world situations in controlled trials. To manage such situations, authors suggest complementing statistical data from RCTs with other kinds of knowledge, which could be gained by way of, e.g., post-marketing monitoring of already authorized drugs (Rocca, Anjum, and Mumford 2020; López and Luján 2022).

The second case study in this category is an example of controversy about if and how to *substitute certain scientific methods used in regulatory science with other methods that are considered more suited*. This concerns the limitations in the use for regulatory purposes of standard scientific methods, meaning methods commonly used in knowledge-oriented science, as well as the technical, regulatory, economic, and social advantages of turning to ‘non-standard’ scientific methods for regulation-related data generation. These controversies commonly revolve around the limited suitability of many standard methods in regulatory decision making due to their significant resource and time requirements. In other words, the tension in this case is related to the question of how to operationalize the

regulatory process, and how to make it more efficient in order to allow for effective decision making. The reliance on methods that are designed to produce data to the highest possible scientific standards can easily make regulatory decisions impractical (Cranor 1993). A typical example is the one of possible health and environmental effects from chemical substances. The large number of such substances on the market, as well as the constant market introduction of new substances make it extremely difficult to study in detail the health and environmental effects of all those products, in order to decide which of them are in need of being regulated (NRC 1983). From this standpoint, a viable regulatory process for chemical substances, in order to be useful to protecting human health and the environment, and given the limited human and material resources, must find ways of analyzing large numbers of such substances in a relatively short time span. Doing so means the application of scientific methodologies that allow for the generation of data in a timely fashion, even if the quality of the resulting data is lower than optimal (Cranor 1995, 2011).

Thus, a number of regulatory agencies –in toxicology trials and chemicals regulation– have turned to non-standard scientific methods, including Short-term tests, Weight-of-the-Evidence analyses, Structure-Activity Relationships, computational modeling and simulation, etc. (Blaauboer et al. 2016; NRC 2007; Krewski et al. 2020). All those non-standard methodologies allow for the testing of a larger number of (chemical, potentially toxic, etc.) substances in a shorter period of time and with fewer resources. Thus, they are supposed to contribute to the ultimate objective of regulation, the protection of human health and the environment, even if the quality of the data they provide is lower than the one of data from standard methods.

To sum up, in our first case study we have identified arguments for improving clinical trials, in order to counteract certain methodological limitations that might limit their usefulness in pharmaceuticals regulation, without however questioning the clinical trial as the standard method for generating regulation-relevant data in pharmacology. In our second case study, a similar point is made, but the argument is to substitute certain scientific methods (that seem better suited to the regulatory environment) for others.

6. Discussion

Our classification of varying types of methodological tensions in regulatory science, as well as related controversies, shows that such tensions can adopt multiple forms and have diverse origins. They are the result of factors that in some cases can be considered *internal* to regulation, while in others clearly are *external* to the specific regulatory process, or even to regulation in general.

The various case studies make clear that the tensions that we have identified in regulatory science are, above all, related to *non-cognitive* factors. They involve, to a lesser

or stronger degree, varying points of view with respect to certain aspects of the regulatory process, i.e., they involve (non-cognitive) attitudes, values or beliefs.

This is borne out by our case studies:

1) Overall justification for adopting a particular regulation in the first place, in our example, health claim regulation. What is the ultimate aim of health claim regulation: a) to protect individual food consumers by any means from false (non-effective) health claims (so they do not waste money on such claims, nor rely upon them for their health), or b) to facilitate the potential contribution of health claims to public health (by trying to strike a balance between, on the one hand, demands for conclusive data and, on the other, a sufficiently large supply of officially approved health claims)?

2) Differences in regulation between GM and non-GM products. Are GM products in some way 'essentially different' from non-GM products, so as to justify a separate regulatory regime, even if that might negatively affect the development of a GM industry? Or, for regulatory purposes, is it more adequate to consider GM products similar (equivalent) to non-GM products, so as to not unduly affect innovation and product development, unless a clear-cut difference in their properties can be shown to exist?

3) Animal protection. Which of the following two points of view is to be privileged, a) protecting animals from being killed in order to generate regulation-relevant data (even if this means using novel methods for data generation that potentially could impact the quality of the data that underpin regulatory decision making, and thus negatively affect protection of human health and the environment), or b) protecting health and the environment on the basis of *in-vivo* data whose reliability and quality can be considered well established, even if this implies the routine use of animals?

4) Industry influence in science. Is it preferable to minimize industry influence on data generation by any means, including potentially contentious interventions (like correction of industry bias by applying an across-the-board correction factor)? Or is it better to let industry innovate without any restrictions (including sponsoring regulation-relevant research), even if that might lead to bias?

5) Limitations of RCTs. Even though some of the questions related to the methodological limitations of RCTs might in principle be resolved by scientific knowledge, in most cases this will not eliminate the need for a judgment involving non-cognitive factors. As an example, more and better scientific data might certainly contribute to answering the question if a particular RCT is able to correctly mimic a particular real-world situation. But such data are very unlikely to provide a definite answer. That is because in the day-to-day (real world) regulatory use of RCTs, generating such data for each individual case would most likely be prohibitively resource-intensive. Thus, a judgment cannot be avoided. The same argument applies to other issues, like the question if statistical evidence suffices, or if an explanation is warranted. In other words, a judgment (involving at least some non-cognitive factors) will always be necessary.

6) Standard vs non-standard methods in data generation. Is it more adequate to always ground regulation in high-quality data that provide an utmost degree of certainty for regulatory decisions, in order to minimize any unwarranted negative impacts for industry, consumers, and the larger economy from potential over-regulation? Or is it more important to be able to generate data on as many products as possible (even if data quality is lower than in the alternative case), in order to regulate all those products that might warrant regulation, despite the possibility of some of those regulatory decisions being unnecessary? In other words, which of the following two risks do we prefer to minimize, a) slowing down the protection of health and the environment, or b) negative impacts on innovation and economic growth?

As our case studies make clear, most of the relevant underlying factors are non-cognitive ones. Taking a decision about which of the respective two alternatives to prefer in each of the case studies is not straightforward. And scientific data do not provide a simple answer. Rather, deciding between the two alternatives involves a judgment in which non-cognitive factors play an important, or even decisive role. In some of the examples, like for instance case studies 2 (GM regulation) and 5 (limitations of RCTs), the scientific aspect might, at least under certain conditions, take on more relevance than in the other cases, in the sense that more scientific data might facilitate a decision; but in the end closure still depends on adopting a particular point of view.

In sum, given the pervasive relevance of non-cognitive factors, it is important that value-related issues, if possible, be made visible in all of the phases of a regulatory process. If such choices remain implicit, the outcome of a regulatory process is more likely to lead to controversy.

7. Conclusions

Controversy in regulatory science –as a general rule– has to be resolved on the *non-cognitive* level. This means that in most cases the typical approach in knowledge-oriented science for achieving closure, based on an appeal to cognitive factors, is either not available in regulatory science, or is insufficient for resolving these kinds of tensions. As our case studies show, controversy over non-cognitive factors can involve differences of points of view with respect to the perceived objectives of a regulatory process, its desired or predicted outcomes and their respective impact on various stakeholders, as well as the justification for deciding to regulate a particular product or process in the first place. None of these controversies can be resolved simply with the concourse of more or better scientific data.

Thus, the main difference between trying to achieve closure in regulatory science, as opposed to knowledge-oriented science, lies in the different role of non-cognitive factors.

In knowledge-oriented science, the most common recourse for resolving tensions with respect to methods and data is the appeal to cognitive arguments, including procedures like peer review or widely-recognized best practices. In regulatory science, in contrast, due to the predominant importance of non-cognitive factors, these kinds of cognitive arguments in most cases do not carry much weight.

This also applies to cases in which similar tensions can be observed in both knowledge-oriented and regulatory science (like, for instance, debate on the question if some of the current New Approach Methodologies are able to produce data with a level of quality that is comparable to more traditional ways of data generation in science, be it knowledge-oriented or regulatory science). However, resolving these tensions in the realm of regulatory science still requires addressing the non-cognitive factors in play.

There is a dynamic aspect to the tensions in regulatory science, too: they evolve in response to changes in, for instance, the development of new scientific methods. In several of our cases one of the driving forces is scientific-technological development (development of new methodologies), because several of the non-cognitive objectives (for instance, reduced animal use or increase in efficiency and speed of regulation) could in practice not be entertained without the existence –or promise of existence in the short and medium term– of alternative scientific methodologies.

The important role that non-cognitive factors play also explains why it is common for regulatory processes in different jurisdictions to regulate the very same product or process in different, even radically divergent ways (for instance, GM products in the EU as opposed to the U.S.); or that there are regulatory processes in which stakeholders may argue for the application of standards, methods or objectives that are fundamentally distinct from the ones currently being applied (e.g., health claim regulation in Europe).

Our discussion shows that the tensions that we have identified here have to be considered a normal, even an inevitable aspect of regulatory science. Importantly, there is no obvious and universal approach to managing these tensions. They depend on agreements, bargains and compromises that the relevant social actors may enter into with respect to the non-cognitive objectives of a particular regulatory process.

In sum, what ought to be clear is that methodological tensions of the type we have identified in our case studies, as well as any related controversy as to the operationalization of regulation are typically not the result of insufficient scientific data or knowledge. Rather, they have to be considered an integral part of regulatory science that no amount of ‘science’ would be able to resolve.

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