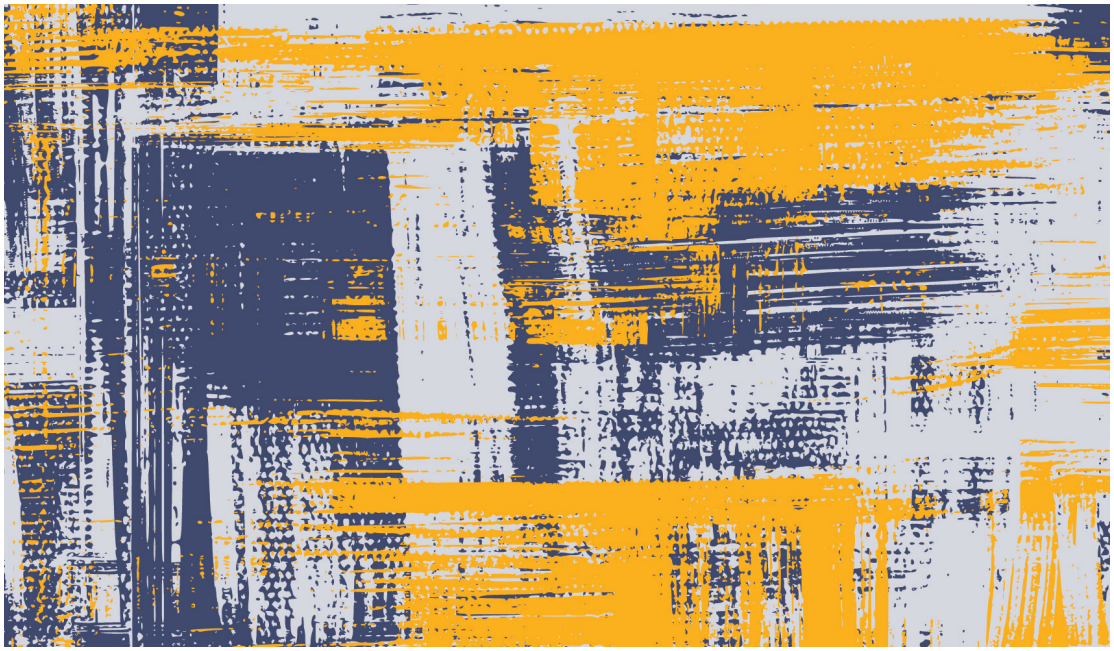

Relianomics: A proposed framework for the assessment of the societal, economic and efficiency impacts of regulatory reliance pathways

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Executive Summary

Background: Regulatory reliance as applied to the medicines authorization process is seen as an efficient means to tackle the increasing workloads faced by national regulatory agencies (NRAs), which have expressed a strong desire to optimize their activities. However, a comprehensive methodology to understand and characterize the benefits, limitations, and return-on-investment of implementing or practicing a reliance pathway by a regulatory agency has not yet been developed. Work to date has focused on "how" to best implement reliance but has not generally focused on understanding the "why" to implement reliance through its measurable impacts. This analysis lays the groundwork for the proposed concept of "relianomics", which we define as a structured framework for the assessment of the impact of regulatory reliance pathways on regulatory, economic, societal, and other systems.

Considerations: We performed an integrative literature review using electronic databases, supplemented by grey literature searched on web sites (reports, position papers, workshop summaries). A total of 36 documents were selected and categorized for analysis: 23 primary articles and 13 reports. These were reviewed and their approaches to assessing the real and potential impacts of reliance and the metrics to measure them were identified. For regulatory efficiency, favorable impacts were categorized into the following domains: work efficiency, shortened timelines and increased collaborations, which were characterized by improved NRA efficiency, enhanced NRA capabilities, improved access to medicine, higher quality regulatory actions/decisions, increased collaboration, and pharmaceutical market growth. Unfavorable impacts included unintended consequences based on secondary reliance and the possibility of relying on regulatory decisions where there was a significant risk-based recognition of uncertainty regarding the product's safety and efficacy. Few resources described empirical measures (metrics) that could be used to assess the impact of the use of reliance. These results underscore the need for a systematic framework approach to assess the return-on-investment of reliance, the core of which is provided herein. While we have identified consequential impacts of reliance, further contributions to this framework are needed to ensure a robust approach to relianomics.

Background

Regulatory organizations are faced with a mosaic of ever more sophisticated drugs, a globalizing pharmaceutical market, and limited human and financial resources[1]. This incentivizes national regulatory authorities (NRAs) to make efficient use of available resources through collaborating with trusted NRAs by relying on the trusted NRA's work and expertise, a process termed *regulatory reliance*.

Regulatory reliance is considered a twenty-first century best practice as promulgated by the World Health Organization's Good Reliance Practice guideline[2]. Regulatory reliance allows NRAs to use work performed or decisions taken by trusted NRAs in other countries to inform their own decisions and assessments. It is a strategy that seeks an optimal use of resources which can span from information sharing and joint assessments, to unilateral or mutual recognition in both the pre- and post-approval

periods. Reliance can be used in the areas of clinical trials, inspections, and medicine authorizations. Some forms of reliance (e.g., unidirectional reliance such as decisions made based on the use of the Certificate of Pharmaceutical Product) have been used globally for decades.

When an NRA is confronted with the decision to adopt regulatory reliance practices, it should do this in the context of the needs and characteristics of its legal, national health and regulatory systems[3,4]. Considering existing capacities, regulatory systems' needs and how reliance can complement these capacities to drive efficiencies should be the basis for deciding on when, how, and to what extent to adopt reliance-based regulatory pathways[3]. In response, the desire to implement regulatory reliance has seen a sharp increase over the past decade and is generally regarded as a smart and efficient way of regulating medical products[1].

Consequently, international public health institutions including the World Health Organization (WHO), the Bill & Melinda Gates Foundation, Pan-American Health Organization (PAHO), Asia-Pacific Economic Cooperation (APEC), The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the International Coalition of Medicines Regulatory Authorities (ICMRA) encourage NRAs to implement reliance-based pathways for the assessment of medicines with considerable attention given to "how" to best implement reliance-based pathways into the work stream of NRAs. While these guidelines provide invaluable guidance as to how to implement reliance, these activities are based on the intuitive expectation that reliance always has favorable net effects. These guidelines, therefore, have not generally focused on understanding the "why" to implement reliance through an assessment of its measurable impacts.

Being able to quantify the impact of regulatory reliance on public health, on economic health, on agency efficiency, and on agency resource utilization would help the larger community recognize the value of this approach to regulation.

WHO encourages NRAs that use reliance pathways to "specifically measure" the impacts of reliance by establishing metrics related to regulatory decision-making such as review times, the number of products reaching the market, costs saved, and redirection of resources to areas of higher regulatory risk[4]. However, these positive measures need to be validated and formalized with additional guidance provided to the authorities on their implementation, keeping in mind that the relevance of such measures will depend on the type of reliance pathway used by an agency. Conversely, measuring the limitations and unfavorable impacts has not been emphasized. There is, therefore, a need for agreed-upon metrics to determine the extent to which these pathways are beneficial in a specific setting, to provide support for where reliance may be most applicable, and to assist agencies to identify areas for optimization. Being able to quantify the impact of regulatory reliance on public health, on economic health, on agency efficiency, and on agency resource utilization would help the larger community recognize the value of this approach to regulation[5].

The idea of monitoring the effects and benefits of reliance on an agency's activities is sound, but in practice quantitative analyses of the return-on-investment (ROI) of implementing reliance pathways

are rare and inconsistently described. Additionally, the suggested metrics typically focus on favorable effects of reliance while understanding potential unfavorable impacts has been limited and thus has not provided a complete picture of the ROI of reliance. Furthermore, a comprehensive understanding of the broader impacts that practicing reliance may have outside of the regulatory agency (e.g., on the public health of a country, the economic impact on the nation or region) does not exist.

Although the overarching theoretical favorable impacts of practicing reliance have been widely discussed, given the lack of study on the overall ROI of using reliance-based regulatory pathways, decision-makers may find it challenging to objectively determine the benefits of implementing or continuing their practice of regulatory reliance. To address this, we herein propose an approach we term "relianomics": a structured framework for the assessment of the impact of regulatory reliance pathways on regulatory efficiency, economic, societal, and other systems. The aims of this study are to establish key elements underlying relianomics through a targeted review and analysis of publications and public documents that describe the empirically established and the theoretically suggested impacts of reliance and to suggest a process for the implementation of a relianomics framework.

Assessment Process

We performed an integrative literature review using electronic databases including MEDLINE and Google Scholar, supplemented by grey literature searched on web sites (reports, position papers, workshop summaries). The search was performed to identify a body of literature published between 2011 and April 2022 that discussed the real and potential impacts of using reliance-based regulatory

Table 1.
Summary of potential favorable and unfavorable impacts of reliance based on published observations

Effects	Potential impacts (number of documents)
Regulatory Efficiency ***Favorable effects*** *Work efficiencies*	Efficient use of resources[14] Focus on prioritized national activities[10] Less duplication of efforts[8] Lightens workload[6] Increased internal expertise[3]
Shortened timelines	Faster access[10] More attractive to industry[3] Quicker response to health emergencies[2] More generics, lower costs[1]
Increased collaboration	Access to external expertise[7] Higher quality regulatory outcomes[4] Builds mutual trust with decision transparency[4] Increased access to data[2] Strengthening/convergence of global regulatory system[2] Better market surveillance[1]
Unfavorable Impacts *Insufficient Decision Support*	Inheriting flawed approvals from reference agencies[2] Unintended secondary reliance[1] Insufficient MOUs/Confidentiality Agreements[1] Need for translations/translators[1]

pathways, using the search string: (regulatory reliance) OR ("regulatory systems strengthening"). Titles and abstracts were reviewed, excluding results unrelated to regulatory science. Furthermore, guidelines, position papers, and reports on reliance from the WHO, PAHO, IFPMA, EFPIA, and CIRS were also assessed.

Documents were reviewed for mentions of the known, likely, or theoretical impacts of practicing reliance. Impacts were defined as any effect of practicing reliance on any parameter, ranging from hypothesized to empirically demonstrated effects. Each impact was assigned a standard term (e.g., "Efficient use of resources"). No impacts were established a priori. An impact was counted once per document. The number of unique documents in which each impact was described was determined to assess the frequency with which the impacts of reliance were mentioned. To begin to formulate a categorization scheme for the impacts we expected to observe, we created the following high-level categorizations and sub-domains: Regulatory Efficiency: favorable impacts (domains: work efficiency, shortened timelines and increased collaborations); unfavorable impacts (domains related to insufficient decision support and knowledge detriment); Economic impacts (encompassing the broader direct and indirect effects that practicing reliance may have on a country's economy); Societal (e.g., effects on medicine access, public health;) and other impacts. If a document presented empirical evidence relating to impacts of reliance, the metrics used were identified and linked to the impact.

Observations

We identified 392 articles that addressed reliance. Of these, 36 met criteria for assessment (specifically describing the known, likely, or theoretical impacts of practicing reliance);[1-36] 23 of these were primary citations for one or more (in)direct impacts of reliance that are, or could potentially be, generated due to an NRA practicing reliance. In addition, 13 publications/reports/position papers were identified that discussed details of the impacts of reliance from WHO[2,4,32], PAHO/PANDRH[3,7,15], IFPMA[6], CIRS[28, 33-36] and EFPIA[29]. Of the observed impacts, 15 were considered favorable and 4 described unfavorable impacts. **Table 1** provides details of the impacts by domain.

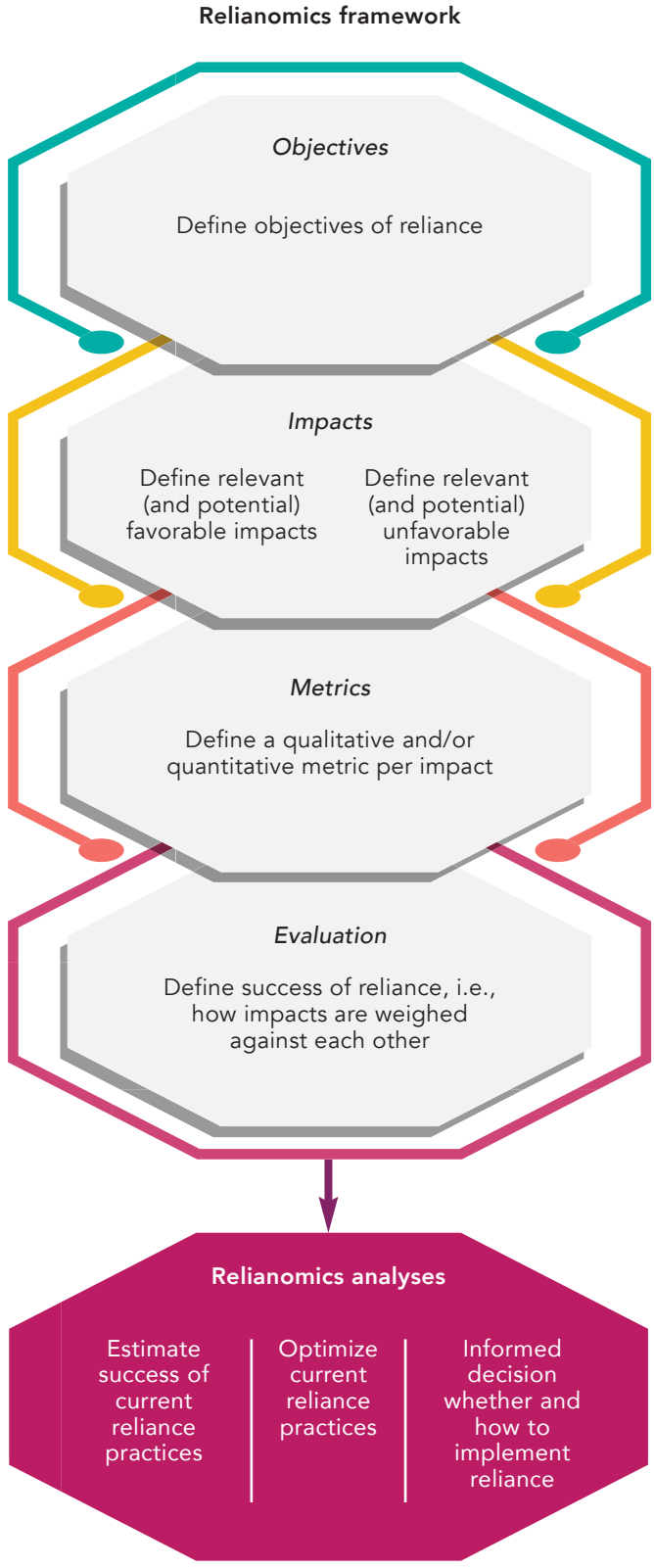
Direct favorable effects of reliance generally related to processes within NRAs, while the broader impacts of reliance related mostly to potential improvements to public health in the form of better (faster, more, or more appropriate) access to medicines along with "higher quality" regulatory action.

Favorable Impacts

Direct favorable effects of reliance generally related to processes within NRAs, while the broader impacts of reliance related mostly to potential improvements to public health in the form of better (faster, more, or more appropriate) access to medicines along with "higher quality" regulatory action. Economic impacts were also reported. Described effects and impacts were:

Effects on work efficiencies: Reliance activities were found to have a multitude of favorable impacts on processes that take place within NRAs. These included improvements in efficiency and enhancing NRA capabilities. Relying on reference NRAs for scientific assessments or site inspections theoretically reduces the amount of duplicated work and lightens

Figure 1.
A simple framework for the use of a relianomics approach



the workload for the relying NRA, allowing it to accomplish more activities, especially local activities with high public health importance for which they cannot use reliance, with a similar amount of resources[8,19].

Effects on review timelines: We observed that reliance can shorten review timelines[33], resulting in favorable impacts on medicine availability[13], lower costs of drugs through multi-product competition (an economic impact)[10], better ability to deal with emergencies by mobilizing resources or ensure timely approvals in case of drug shortages or health emergencies[4,12,15]; further, the shortened timelines could strengthen the pharmaceutical market by attracting industry[8,10,13].

Increased collaborations: Besides reducing workloads, practicing reliance is presented as a means to enhance NRA capabilities by strengthening in-house competence through learning by collaboration and work-sharing[6], as well as being a means to address gaps in technical skills by providing access to external expertise[18], and better market surveillance through access to comprehensive data resulting from information sharing with other NRAs[13]. A broader impact of reliance on the economy is as a catalyst for innovation through building trust between NRAs, thereby supporting increased regional, continental, and international efficiency and alignment[21].

Unfavorable Impacts

Some authors addressed the potential downsides of reliance. Importantly, they cite the potential limitations of chains of 'secondary-reliance', in which NRAs might rely on reference NRAs that, in turn, relied on another reference NRA. Since it is often difficult to determine what products were approved through reliance and which were not, these chains of secondary reliance could reduce trans-

parency of decision making and could unintentionally lead to NRAs effectively relying on reference NRAs that they do not formally recognize, albeit through an intermediary trusted NRA[26]. The issue may be compounded if the NRA lacks the capacity to properly monitor new information with regards to the product safety and effectiveness and potentially retract the approval in light of new evidence[25,26].

Empirical Metrics for the Assessment of Reliance

The limitation to assessing the ROI of reliance was seen in that the use of specific empirical evidence relating to measuring the impact of reliance was discussed in just seven publications[7,20,22,23,30,32,35]. The specific types of measures described in these sources were: number of yearly authorizations; change in size of market authorization backlog; review time/time to market; time between reference and reliance approval; market price change after approval; cost savings; efficiencies in the number of products reaching markets; a redirection of scarce resources to areas of higher regulatory risks. Guidance for collecting, analyzing or holistically applying these metrics to a ROI was not observed.

The Relianomics Building Blocks

Figure 1 presents the building blocks for a "relianomics" framework aimed at assessing reliance pathways that are either being considered for implementation by an NRA or where an NRA desires to assess their existing reliance practices. A relianomics analysis should encompass demonstrated and potential impacts of practicing reliance supported by their corresponding metrics. In sequence, it should include 1) a definition of the objectives that reliance should achieve from the decision-maker perspective, 2) a categorized overview of the potential favorable and unfavorable impacts of practicing reliance, 3) one or more metrics for each impact to measure qualitatively and preferably also quantitatively and 4) guidance on how to use these measurements to guide the assessment of ROI. We recognize that certain impacts may carry more weight than others; ultimately, the relianomics framework should allow the user to value those impacts based on their specific situation.

A relianomics analysis should encompass demonstrated and potential impacts of practicing reliance supported by their corresponding metrics.

The use of a framework built on the characteristics in **Table 1** and the concepts in **Figure 1** would allow policy makers to not only understand what impacts reliance has, but also would enable them to assess whether and how much each impact contributes, and so forming the basis of estimating the actual or potential ROI of a reliance process. In addition to facilitating informed decisions on implementing reliance, such a framework also would enable meaningful comparisons, which are essential to designing better reliance pathways and optimizing existing ones.

While the metrics associated with each impact may be collected by the agency or derived from other sources, they should be standardized as much as possible across jurisdictions to ensure reliability and enable comparisons. Decision makers will need to weigh each

impact as they see fit for their situation, permitting flexibility to individualize the relianomics analyses. This ensures the framework will be applicable across widely varying health-systems and reliance activities.

Reflections

The aim of this analysis is to lay the groundwork for the proposed concept of "relianomics", which we define as a structured framework for the assessment of the impact of regulatory reliance pathways on regulatory efficiency, economic, societal, and other systems. We have begun by developing the key elements underlying relianomics through a targeted review and analysis of publications and public documents.

Our analysis identified a spectrum of ideas about the impacts of reliance, ranging from empirically tested impacts to author's hypothesis. The list that resulted from this analysis (**Table 1**) represents currently recognized consequential and important impacts of reliance. Importantly, we observed that the focus of publications related to reliance pathways has been on the observed or potential benefits, despite the relative paucity of empirical evidence to support these favorable impacts. However, it cannot be interpreted as an exhaustive list that reflects a comprehensive description of all the potential impacts of reliance. Rather, we look forward to expanding this list through interviews, surveys and other collaborative interactions.

Few of the reports described unfavorable impacts when planning or using reliance pathways. Yet, barriers to reliance exist[28,36]. For example, the possibility that reviewers believe that their technical expertise might not be maintained because they are not being intellectually challenged when conducting a reliance assessment and the consequent loss of internal knowledge and expertise were not a focus of publication. Nor did we observe discussions of limitations resulting from the lack of legal frameworks (e.g., regulations that allowed or restricted the use of reliance). Conversely, while it is generally presumed that there are benefits to approaches such as worksharing based on timeline metrics, we did not observe empirical research focused on the specific benefits that we expected to be associated with joint or collaborative worksharing registration processes such as enhanced knowledge exchanges, cross-functional training, and ways to optimize review procedures tailored to reliance assessments.

Another potential limitation of reliance is that it comes with the risk of relying on regulatory decisions from reference agencies where at the time of the decision, there was a significant local risk-based recognition of and acceptance of uncertainty regarding the product's safety and efficacy, which may not be the case in the relying jurisdiction. This may for example occur when a new advanced therapeutic medicinal product is targeted to a rare disease with a limited affected population, or in the case of an emergency use or conditional authorization. Coupled with a paucity of details about the decision (e.g., limited details may be provided in public assessment reports), this could lead to NRAs approving products whose benefit-risk profiles are incompletely characterized for their local population, or for which additional patient experience could reduce regulatory uncertainty. In these situations, in which requisite data is redacted or otherwise unavailable, NRAs may find it challenging to use reliance-based pathways. This may also apply when, for example, a country is receiving a version of a product that differs from the version reviewed/inspected by the reference agency and for which a clear description

of the relevance of the differences or of the "sameness" of the product is not available.

Economic impacts (either favorable or unfavorable) of reliance were the least mentioned effects and were centered around market growth and collaboration. The case for liberalizing trade in health-care products is strong; facilitating trade has been linked to improved availability of health-related products such as vaccines which, in turn, would boost usage[31]. We did not observe research on the wider economic effects of reliance (e.g., improved medicine access leading to decrease in lost workdays, with more consistent contribution to the tax base). Similarly, no primary evidence was observed for the societal impact of reliance (e.g., the benefits resulting from a widened formulary and earlier patient access to more varied products, improved health status due to earlier access). While regulators may not see these impacts as being directly related to their daily activities, we believe that they are important components of an holistic view of the impact of reliance.

The foundational list created herein is derived from documents that, even though they discuss "how" to best implement reliance, were generally not focused on understanding the "why" to implement reliance through its measurable impacts. A limitation to assessing the impact and ROI of reliance is seen in that the use of empirical evidence relating to impacts of reliance was seldom discussed (7 publications), and metrics that enable the regulatory, economic and societal assessment of reliance pathways are scarce despite WHO and NASEM[37] recommending the impact of reliance pathways to be monitored and evaluated using such metrics[4]. While these articles expressed the perspectives of a mix of stakeholders (e.g., innovative pharmaceutical industry, regulators from mature and maturing agencies, academics), the perspectives of other stakeholders (e.g., patients, procurers, public health experts) could provide additional dimensions to the relianomics framework.

More robust guidance based on the concept of relianomics can support decision makers' ability to objectively consider implementing reliance or evaluating the impacts of their existing reliance pathways through this form of regulatory impact assessment.

This imbalance illustrates that it remains challenging to estimate the ROI of implementing or using reliance-based regulatory pathways because their impacts may not be comprehensively understood and often remain theoretical in the absence of comprehensive validated metrics or empirical evidence to support or assess them. NRAs have a strong desire to benefit from the use of regulatory reliance pathways, which they are pursuing rapidly. More robust guidance based on the concept of relianomics can support decision makers' ability to objectively consider implementing reliance or evaluating the impacts of their existing reliance pathways through this form of regulatory impact assessment.

The aggregation of favorable and unfavorable impacts of reliance, coupled with informative metrics provided in a consistent format across agencies will support meaningful performance comparisons of different reliance pathways. These types of comparisons will support the goal of designing more efficient and effective reliance pathways based on best practices and by identifying areas for

improvement for the reliance approach, if it is not having the desired impact or deciding which approach to implement based on local needs. It can also guide an agency to evaluate which form of reliance pathways will have the desired impact in their jurisdiction.

We realize constructing such a framework, or merely identifying the domains, is challenging and will require considerable investments of time, resources, and stakeholder alignment. Ideas for the types of characteristics that could be integrated into the relianomics framework abound, but have not been well described in the literature (e.g., addressing assessors' acceptance or resistance to reliance, impact on the diversity of products in the national formulary; measuring cultural change within an organization). This study is a key step in compiling a list of regulatory efficiency, economic and societal impacts found in current scientific literature. We hope that our proposed relianomics framework can form the starting point for a consistent approach to optimizing the implementation of reliance-based regulatory pathways and evaluating their various impacts. These observations require expansion through surveys and other targeted data collection interactions, which we hope will be stimulated by this initial research. We believe that a relianomics framework is a necessary evolutionary step for developing our understanding of what efficient and effective regulatory reliance looks like and how its potential impacts should be evaluated. •

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