Regulatory Impact Analysis for the Risk Based Lot Release Policy for Biological Products in Egypt

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Abstract

For public health and lifesaving, timely access to high-quality biological products is essential. However, barriers including resource scarcity, limited human capacity, and complex supply chains impede this goal. National regulatory authorities should enhance their frameworks and move forward for regulatory convergence, harmonization, and enhancing reliance practice in order to address these concerns. A risk-based lot release policy is one of the enablers that ensure implementation of smart regulations and best practices was employed by Egyptian drug authority (EDA) to boost the effectiveness of the lot release framework while upholding safety, efficacy and quality criteria. The legal framework for lot release in Egypt was examined using a regulatory impact analysis method. With a considerable impact on time and cost savings, as well as a better net benefit value, the new risk-based lot release policy has the potential to greatly increase the efficiency of Egypt's LR regulatory system for biological products. Nevertheless, significant challenges and unexpected consequences were also noted, including the need for ongoing capacity building and growing regulatory requirements based on best practices. The findings have major reflections for drug policy makers and regulators looking to enhance their biological product regulatory systems; since the policy's benefits outweigh these possible challenges. This paper offers a full examination of the risk-based lot release policy used by the EDA, Egypt for biological products, assisting in understanding both the benefits and challenges of this approach.

Key words: ***Egyptian drug authority, Reliance, lot release, risk-based, regulatory impact analysis, smart regulations, convergence.***

1. Introduction

In the context of public health protection, regulatory authorities have a key responsibility to ensure timely access to essential medicinal products including biologicals in order to fulfill the right to health. However, there are many barriers to achieve this responsibility due to increasing complexity of supply chain, resources scarcity, and limited human capacity (Roth et al., 2018). In order to achieve the main obligations toward public health, regulatory authorities worldwide have to enhance their regulatory framework and find their way to regulatory convergence and harmonization (Saint-Raymond et al., 2022; Xu et al., 2022). Regulatory reliance is a mechanism

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for proactively enhancing regulatory capability, expanding access to medications, and optimizing resource utilization according to WHO good reliance practice (Gostin et al., 2020). In order to define the optimal model for the reliance mechanism and obtain the greatest regulatory outcomes, regulatory authorities are increasingly using risk-based approaches considering factors such as the degree of resources and knowledge offered by the national regulatory authority (NRA), the nation's requirements and priorities in terms of public health, and potential for reliance (McAuslane et al., 2023).

In Egypt, the regulatory environment for biological products has been undergoing significant changes in recent years to adopt reliance models in most of regulatory functions. One of these important and unique regulatory functions concerning biological products is the lot release (LR) function. A lot release process is used to review crucial manufacturing and testing data and carry out independent testing at regulatory authorities for critical quality attributes regarding the safety and quality of biological products especially vaccines before each batch is marketed. (Gupta et al., 2015). According to WHO, it is crucial to conduct an independent assessment of critical data from each lot of biological products specifically vaccines to ensure the consistent quality of each manufactured lot (WHO Technical Report Series 978, 2013).

In 2020, the lot release system inside the Egyptian drug authority (EDA) has been transformed and a new risk-based policy has been implemented to improve the efficiency epurpose of this study is to examine the regulatory impact of the newly implemented risk-based lot release (RB-LR) policy implemented by the EDA, this will be performed using regulatory impact analysis (RIA) which is a systematic approach used to assess the benefits and costs of a new or an existing regulation (Kurniawan et al., 2018a). We will analyze the impact of the policy on the pharmaceutical industry, regulatory agency, and public health. The findings of this study will provide insights into the effectiveness of the policy and identify areas for future & continuous improvement.

2. Methodology

This study provides a comparison of the newly implemented RB-LR policy since October 2020 till now and the old one implemented before October 2020, through a comprehensive review of policy documents & regulatory framework in Egypt using a set of evaluation methods according to RIA approach.

2.1 Regulatory impact analysis (RIA)

Regulatory impact analysis is performed to assess the benefits and costs of the old and new policies. An evaluation framework based on the RIA approach, (Jonski & Rogowski, 2023; Kurniawan et al., 2018b), was used to assess the consequences of the risk-based lot release policy according to the following steps:

- Regulatory problem identification
- Definition of LR policy
- Identifying the regulatory alternatives
- Comparing the regulatory alternatives
- Cost-benefit analysis of regulatory alternatives
- Stakeholders consultation to monitor efficiency

Cost benefit analysis of regulatory alternatives

Cost benefit analysis was performed through determination of direct cost and time savings and total impact on costs and benefits (direct & indirect) as follows; cost savings; time savings; impact on regulatory cost and benefit; risk based lot release policy in Egypt survery.

Cost savings (Direct cost)

To determine the direct cost savings from the new RB-LR policy, the study team calculated the average cost per batch analysis and the average number of batches received annually (from 2020-2022). They then calculated the annual cost of analysis according to each policy (the old and new one), and the significance between the two results was determined.

Time savings (Direct benefit)

The average time for release for both the old and new RB policies was calculated, and the significance between the two results was evaluated in order to determine the impact of the new RB-LR policy on the time required for product market access as a direct benefit of the adopted method.

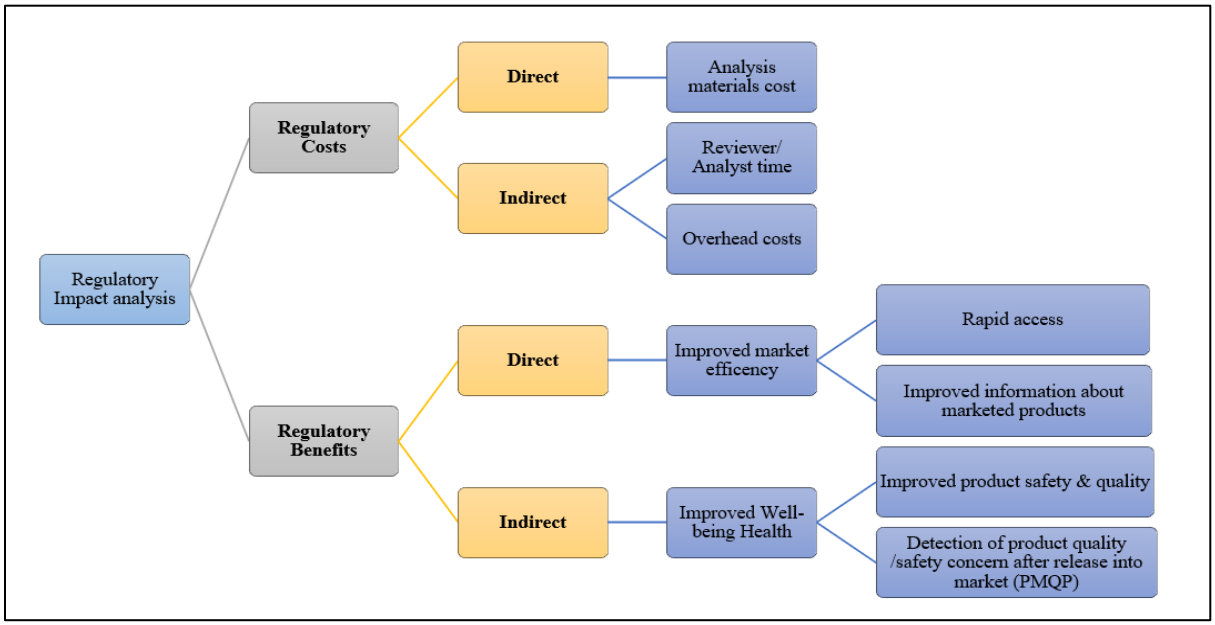

Fig.1. Regulatory cost –benefit map

Impact on regulatory cost & benefit

The economic impact of regulatory policies is important from the regulator, industry and society perspectives. A full cost-benefit analysis for the direct and indirect impact was performed to determine the regulatory alternative that provides the highest net benefit.

First, the direct and indirect regulatory costs and benefits associated with the lot release function were determined. (See Figure 1) Second, the study team created an effect assessment scale to quantify the policy cost/benefit impact and utilize it in the cost-benefit analysis (CBA) calculation. The net benefit value for each alternative impact was then calculated by subtracting the estimated impact for costs

from the estimated impact for benefits. Finally, the cost effectiveness plane (CEP) was utilized to find the optimum choice to execute. (See Figure 2)

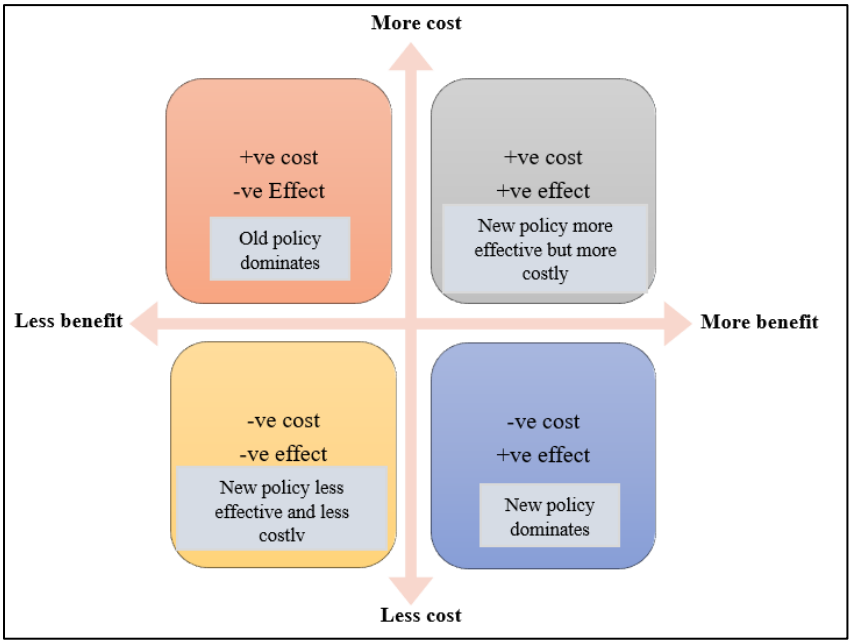

Fig.2. Regulatory cost –benefit map

Risk based lot release policy in Egypt survey

To obtain more insights into the policy's strengths and weaknesses, we also investigate local stakeholders' responses through a specially designed questionnaire administered online. The survey was in English. The survey consisted of twenty-one questions. It consisted of five major sections; section one was about the respondents' demographics. Section two to evaluate respondents understanding of RB-LR policy, section three to determine impact of RB-LR policy implementation in Egypt, section four aimed to check the challenges in implementing RB-LR policy, and finally section five to get respondents suggestion for any further improvement in the lot release process. The survey was designed by the research team based on their regulatory experience and the information collected from relevant stakeholders through direct interviews. It was content validated by regulatory experts as well it was published for pilot phase on small scale to gain information to improve the efficiency of the final survey version before being disseminated to the respondents.

2.2 Statistical analysis

Statistical analysis was carried out using Minitab (2014) statistical software, version 14 (Minitab Incorporation, State College, Pennsylvania, USA). Student t-test was used to determine the significance between results. P-value < 0.05 was considered statistically significant.

3. RIA Study Findings

3.1. Regulatory problem identification

By the beginning of 2020, the research team discussed the obstacles that faced the availability of biological products for the Egyptian population and the obstacles that impeded accelerating the release of these products and their availability in the market with both internal and external LR stakeholders multiple times, and as a result of these discussions, a significant amount of data and facts had been mapped in the lot release era., which have then been condensed into the formulation of the primary identified regulatory problem as follows: "*Biological products including vaccines often require independent batch release testing before released into market by EDA laboratories. This independent testing may take too long time which impacts the supply and timely access of essential products."* The research team came to the conclusion that the former Egypt's lot release policy did not yet align with the EDA's goals, which specify that the EDA is in charge of assuring availability and rapid access to safe, effective, and high-quality products.

3.2. Definition of LR policy objectives

With the aforementioned assertion, an objective statement for the new LR policy- that will guide the choice of action and is consistent with the strategic objectives of EDA- was created as follows: *To ensure the quality and safety of biological products, EDA should implement LR risk-based approach, which allows for testing, oversight, and the emphasis of products that require more intensive surveillance.*

3.3. Identifying the regulatory alternatives

After analyzing the challenges and concerns that were gathered and reviewing the lot release guidance, regulations, and best practices that are followed globally, the research team arrived at two potential alternatives and their consequences to deal with the previously mentioned regulatory problem (Table 1).

3.4. Comparing the regulatory alternatives

The two identified alternatives were compared and items of comparison selected based on the WHO independent lot release guideline and the results of the comparison are summarized in Table 1.

3.5. Cost- benefit analysis of regulatory alternatives

3.5.1. Cost savings (Direct cost)

Implementing the new RB-LR policy resulted in an average cost reduction of 35 Million ± 150,000 L.E., which was determined to be a statistically significant difference between the old and new policies' analysis costs, as indicated in Table 2.

Table 1: Comparison between old and new lot release policies

	Old Policy	New RB-Policy
Approach used	▪ All batches undergo document review and sample independent testing	▪ Risk based approach where batches undergo one of the following approaches: 1- Documents review with independent selected testing 2- Document review only 3- Recognition/acceptance of lot release certificates from the responsible NRA/NCL.
Release pathways	▪ Normal pathway ▪ Expedited pathway	▪ Normal pathway ▪ Expedited pathway ▪ Reliance pathway
Testing strategy	▪ Performing all testing parameters	▪ Focusing on value added testing parameters
Time for release	▪ Standard time frame for all products except products with long bioassays that can exceed the standard time frame	▪ Time frame depend on product risk category and release pathway.
Risk assessment	▪ Batch dependent	▪ Product dependent
Quality monitoring system	▪ Premarketing quality monitoring system only	▪ Premarketing and post marketing quality monitoring system
Monitoring consistency	▪ Through trend analysis only	▪ Trend analysis and evaluation of annual product quality report (APQR)
Transparency	▪ No online version available from policy	▪ Both policy and guideline are publicly available on EDA website.

Table 2. Direct Cost-Savings Calculation

Average cost (L.E) /batch analysis ± SD	Average no of batches received/ year ± SD	Average cost of analysis (L.E) / year ± SD (old policy)	Average cost of analysis (L.E) / year ± SD (new RB policy)	Cost savings (*p*-value)
15000 ± 9000	3390 ± 15	51 Million ± 225,000	16 Million ± 75,000	< 0.0001***

*Statistical analysis using student test-*statistical significance at P <0.05*

Table 3: Release Time savings

Average batch release time (days) ± SD (old policy)	Average batch release time (days) ± SD (new RB policy)	Time savings *p*- value
36 ±20	11 ± 8	< 0.025*

3.5.2. Time saving (Direct benefit)

As a direct benefit estimator for the LR policy, the time needed to release a batch into the market was employed. It was discovered that the new RB- policy led to quick market access for biological products, which was shown to be a statistically significant difference from the old one as shown in Table 3.

3.5.3. Impact on regulatory costs & benefits

The net benefit for each policy was calculated using the impact assessment scoring system which adopted from the previously published one (Dumbravă & Vladut-Severian, 2013) shown in Tables 4 & 5, and it was found that the RB-LR policy has a higher net benefit with a low impact on cost and a high impact on benefit. As a result, the new policy will prevail and be the best option for the lot release regulatory framework.

Table 4: Impact assessment scoring system

Impact Assessment Scale	
Scoring points	**Description**
5	Probability of making a high impact on cost/benefit
3	Probability to generate a medium impact on cost/benefit
1	**Probability of making a low impact on cost/benefit**

Adopted from(Dumbravă & Vladut-Severian, 2013)

Table 5: Regulatory impact cost-benefit assessment

		Old policy	**New RB policy**
Costs	Analysis materials	5	1
	Analyst time	5	1
	Reviewer time	1	5
	Overhead costs	5	1
	Total cost score	**16**	**8**
Benefits	Rapid market access	1	5
	Improved information about marketed products	1	5
	Improved product safety & quality	3	5
	Detection of product quality /safety concern after release into market	1	5
	Total benefits score	**6**	**20**
Net benefit score		(-10)	12

Table 6. Survey participants' characteristics

Participants		N (%)
Work Specialty	Drug regulatory affairs	24 (37.5)
	Quality control	13 (20.3)
	Supply chain	8 (12.5)
	Batch release	6 (9.4)
	Quality assurance	6 (9.4)
	Market access	4 (6.3)
	Others	3 (4.8)
Years of Experience	< 1 year	1 (1.6)
	1-5 years	12 (18.8)
	6-10 years	8 (12.5)
	11-15 years	15 (23.4)
	16-20 years	15 (23.4)
	> 20 years	13 (20.3)
Education Level	Bachelor's degree	34 (53.1)
	Diploma degree	2 (3.1)
	Master's degree	14 (21.9)
	Professional degree	7 (10.9)
	Doctorate degree	7 (10.9)
Familiarity With RB-LR Policy	Not at all familiar	1 (1.6)
	Not very familiar	3 (4.7)
	Somewhat familiar	15 (23.4)
	Very familiar	45 (70.3)

3.6. Stakeholder consultation to monitor efficiency (survey results)

In total, 64 participants took the survey. The number of responses per survey question varied due to the survey sections' flow and participant drop-out. Sixty respondents completed the survey in full. Participants' characteristics are summarized in Table 6.

3.6.1. Understanding of RB-LR policy

With regard to the respondents' understanding for RB-LR policy, 64 respondents had some degree of knowledge about RB-LR policy. Among the 64 respondents who claimed some degree of knowledge about RB-LR policy, 10 (15.6%), correctly defined the primary purpose of RB-LR policy that is to focus on ongoing testing of product for which enhanced surveillance is needed as shown in Figure 3.

As for the potential benefits associated with RB-LR policy, 55 (85.9%) out of 64 respondents agreed that the potential benefits of RB-LR policy was to reduce time required to release lots and improve market access of biological products. In parallel, 32 (50 %) respondents confirmed that RB-LR policy reduced costs associated with releasing lots. Furthermore, 30 (46.9%) respondents agreed that RB-LR policy can help in increasing safety and quality of released lot indirectly.

Based on the respondents' opinions, the most important considerations when implementing RB- LR policy will be the product quality (68.8%) followed by regulatory requirements (28.1%), while only

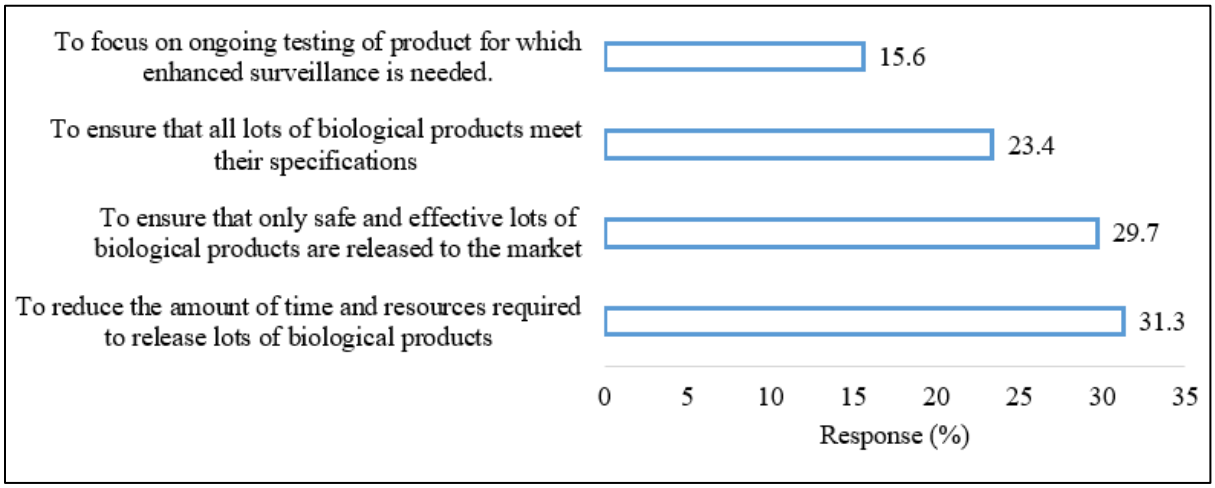

Figure 3. Purpose of RB-LR policy for biological products (n = 64)

(3.1.%) suggested that the manufacturing process is the most important one.

3.6.2. Impact of RB-LR policy implementation in Egypt

According to the survey results, implementation of RB-LR policy in Egypt has many benefits, the first; enhancing market access process for biological products (52 response). The second; by reducing analysis requirements and saving resources (41 response). Third; improving regulatory compliance (34 response). Finally; it increases product quality indirectly through focusing on products that require greater regulatory oversight (17 responses), in regards to different release pathways, respondents agreed that all the three release pathways (Normal, Expedited and Recognition) have a significant impact on biological products release in Egypt.

According to the results, respondents trust that the implementation of post marketing quality monitoring program (PMP) for low-risk category products through RB-LR policy has a meaningful impact and importance for biological products market control in Egypt, 55 out of 64 (86 %), confirmed that PMP implementation is important**.** Furthermore, respondents confirmed (87.5%) that the implementation of RB-LR policy is an effective way of ensuring product quality and safety.

With regards to the impact of RB-LR policy on the respondents' organization, the results indicated that 43 out of 64 agreed that RB-LR policy has enabled faster product release times. In parallel, 39 out of 64 confirmed that it has improved processes efficiency and reduced costs, as well 15 out of 64 agreed that it has resulted in more stringent quality control measures. While only 7 out of 64 found that RB-LR policy has increased the complexity of operations and processes for their organization.

3.6.3. Challenges in implementing RB-LR policy

Regarding the most common challenges respondents faced in implementing RB-LR policy in Egypt, only 7 out of 64 (11%) found that poor communication between release process

stakeholders is the major challenge. The rest of answers were centered around limited resources and unforeseen implementation issues, followed by lack of sufficient training and difficulty understanding principles.

Only 22 out of the 64 responses to the question on how the RB-LR policy affected their organization's quality assurance system were recorded. Some examples of responses included:

- Prompt response to regulatory requirements
- Submission of new APQRs and PMS requirements
- Adaptation of our quality system to the new regulations
- A change control opened for Egypt to include the new requirements
- Reduction in time and effort
- Check accuracy for all documents for all products before submission

3.6.4. Further improvement

The current survey responses provide four critical insights into the factors that would help in improving lot release system efficiency. The first one is the development of an integrated system for tracking post marketing product quality, safety and efficacy information from real world across multiple EDA regulators. The second key factor is the improvement in communication between other regulatory functions. The third one is streamlining of operating procedures and finally continuous investment in training programs for LR employees' capacity building.

According to participants' opinion, RB-LR policy for biological products in Egypt achieves its goals and objectives and most of them were satisfied after its implementation

4. Discussion

All NRAs around the world are now focusing on improving regulatory performance and hastening the pace of regulatory approvals through the implementation of expedited regulatory pathways which allows relying on or recognizing the regulatory decisions of other stringent regulatory authority (SRAs) (Hashan et al., 2022). Recently, NRAs are employing risk-based strategies to define the reliance model for many regulatory functions and to achieve the best regulatory practices (McAuslane et al., 2023; Moeti et al., 2023).

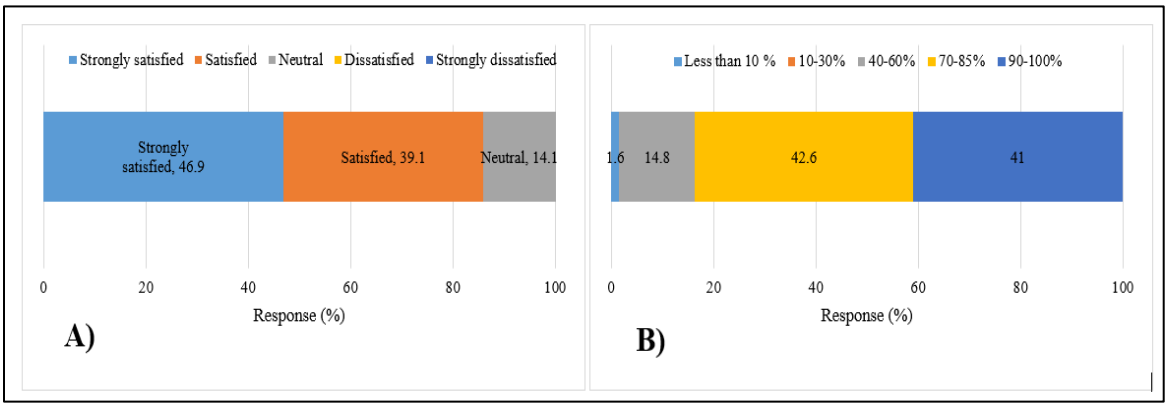

Fig. 2. A) Overall customer satisfaction level after implementation of RB-LR policy for biological products in Egypt (n=64), **B)** Percentage by which RB-LR policy achieves its goals and objectives (n=61).

Using a risk-based approach in regulatory decisions, which eliminates work duplication and concentrates regulatory efforts and resources where they are most required, enables effective use of the available resources and expertise. EDA has introduced the use of risk-based approach in the lot release function for biological products to focus testing on products for which enhanced surveillance is needed and avoid any delay in product supply and market access. In general, the results of this study demonstrated a significant reduction in the time required for batch release with efficient use of available resources. The results emphasized that the newly implemented Egyptian RB-LR policy is a smarter way for ensuring rapid market access for high quality biological products which in line with the previously published data concerning impact of reliance in regulating medical products (Saint-Raymond et al., 2022). One of the areas highlighted in this study was the substantial impact and importance of the post-marketing quality monitoring program (PMQM) for biological product market control in Egypt, with no impact on product supply or market access. These findings were consistent with previously published data suggesting that the post-marketing testing approach provides a one-of-a-kind opportunity to detect quality flaws in products on the market. Furthermore, it can detect substandard/falsified products before they are distributed to populations, and increases patient access to biological products, reduces the danger of drug shortages, and eliminates resource misuse and economic losses (Rönninger & Garbe, 2016).

Alastair J et al. claimed that there are challenges with all forms of reliance. These challenges include a lack of resources due to growing globalization and global complexity, differences in regulatory systems, the length of time needed to develop trust and confidence, and the difficulty of measuring reliance arrangements objectively(Alastair J. Wood and Patricia Cuff et al., 2020). The findings of this work were congruent with the earlier one reported by Alastair J. et al., which found that RB-LR policy implementation presented some challenges that EDA will take into account as it sought to make future advancements.

5. Conclusion

The findings of this regulatory impact analysis have important implications for policymakers and regulators seeking to strengthen their regulatory systems for biological products by ensuring that the best possible science-based evidence, standards, practice and smart regulations are driving the regulatory process, resulting in improved safety, and rapid access. By providing a comprehensive analysis of the EDA's risk-based lot release policy for biological products in Egypt, this research article contributes to a better understanding of the potential benefits and challenges associated with this approach.

6. Recommendation for future work

Although RB-LR policy’s strengths have been noted, there are still certain areas that need development, where the study concluded with a set of recommendations for policymakers and regulators, including the necessity for clear communication, transparency, sharing information and stakeholder engagement, adequate resources and capacity building, and robust monitoring and evaluation mechanisms. Policymakers and regulators can guarantee

that the proper application of risk-based lot release policy for biological products accomplishes its intended goals while minimizing any impact on stakeholders by putting these ideas into practice.

7. Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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