

The Office of Innovation: as core initiative to bolster novel pharmaceutical products-the Cuban approach.

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Abstract:

Regulatory agencies across the Latin American Region have strengthened the regulatory science through the development of new tools, standards and various other related parameters to evaluate and assess safety, efficacy, quality and performance. The former have been implemented to promote and incorporate new drugs and technologies, which still, are a challenge to well-established regulatory frameworks. Furthermore, in today's environment, the existing regulatory framework protecting public's health creates barriers for market entry of novel drugs and medical devices. This article aims to the pioneering work that Cuban Regulatory Agency (CECMED) has been developing with the aim to build a strong regulatory framework geared to accelerated innovation and the successful transition from research and development to clinical development. The Office of Innovation recently established at the CECMED is the first flagship in Latin America and the Caribbean region. Its aim is to play a leading role as a driving force for the national and regional biopharmaceutical innovation. This article will discuss the Office of Innovation its conceptualisation and management taking into account the Latin American regional and national Cuban context.

Keywords: Office of Innovation, novel drugs, novel therapies, regulatory science, Latin American Regulatory landscape

Introduction

Presently, there is vast evidence to show that never before has pharmaceutical innovation had such positive impact and long-term improvements on human health. Lately, on an annual basis, novel drugs and/or their combinations, vaccines against communicable and non-communicable diseases such as cancer, diabetes or orphan diseases are being introduced for therapeutic treatments. Furthermore, the use of the state-of-the-art technologies, such as nanotechnology and other new materials have been emerging¹. The World Health Organization (WHO) has engaged in health innovation to achieve universal health coverage within the context of the Sustainable Development Goals (SDGs). As part of this role, the WHO adopted The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) to promote a completely new conceptualization on innovation and access to medicines. The WHO plan seeks to provide an enhanced and sustainable basis for needs-driven essential health research and development relevant to diseases which disproportionately affect developing countries.²

Further, many innovative drugs during the early stages of development have shown promising evidence, therefore they may be considered as a solution for the treatment of diseases that still have no known cure. However, the skyrocketing costs for developing these novel drugs places at risk the economic sustainability of health services and/or the out-of-pocket expenditures of individuals and families^{3,4,5}. It is relevant to mention the conceptual description of an innovative product. It (i) offers effectively treatment on a particular illness and significant improvements over

existing treatments; (ii) shows verifiable therapeutic opportunities on diseases where there is no effective treatment or in subgroup of patients with unmet medical needs⁶.

On one hand, it is clear that we are witnessing the emerging potential of innovative medicines, therapies and technologies to help advance population health and quality of life, extending life-expectancy, reducing disease progression, and at times posing a higher probability of improving the quality of life of patients or curing a disease. On the other hand, regulatory gaps are frequently being challenged, to addressing the implementation of optimized regulatory pathways in order to obtain a marketing authorization. Moreover, improperly clinical study designs, untimely, or unnecessary clinical studies and/or delay in regulatory reviews due to administrative requirements from Regulatory Agencies creates unnecessary barriers to market entry and patients access to new drugs or therapies⁷.

Indeed, it is clear to state that novel regulatory initiatives and approaches are required to stimulate innovation in order to provide the appropriate incentives for research and development activities which lead to innovative medicines that effectively target real therapeutic needs. The purpose of this publication is to address the pioneering work being developed by the Cuban Regulatory Agency (CECMED) focused on build a regulatory framework to speed innovation linked to expertise and regulatory capacities for translating scientific innovations into effective therapeutic medical specialties. Toward this goal, the establishment of the CECMED's Office of Innovation becomes the first of its kind in the Latin American and the Caribbean region to help facilitate the exchange of expertise through an early dialogue between

Researchers and the Regulatory Agency, supporting a science-based regulatory environment, also spear both national and regional biopharmaceutical innovation. We will further discuss the conceptualisation and management process of this novel initiative taking into account both the regional and national context.

Office of Innovation: developments within the international context

Health Innovation is inherently linked to change, optimization, improvement and access. According to the WHO, the development of new or improved health policies, systems, products, medical devices, technologies, services and delivery methods which improve people's health adds value in the form of improved efficiencies, effectiveness, quality, safety and/or affordability ². Health Innovation can disrupt the status quo of existing way of doing things. It may also involve initiatives to address market failures, regulatory gaps through a holistic approach to build new synergistic and strategic partnerships increasing competitiveness of the research and development process.

The global regulatory landscape has evolved into a process of regulatory diversification, due to the urgent needs for more flexible and less costly regulatory requirements, without compromising the quality and safety of innovative products. Some countries have established Innovation Offices as a first step towards a regulatory innovation pathway. Innovation Offices may have different names, structures and functions, but they all aim to provide regulatory clarification to health providers seeking to offer innovative products and services ⁸.

In 2015, Japan shortened considerably the drug development process, allowing investigational medicinal products, such as gene therapies and regenerative medicinal products to be marketed on a conditional basis after an initial stage of clinical testing in a small cohort of patients ⁹. Similar changes have also been observed in the USA, where modifications introduced on the regulatory framework have focused on the need to accelerate the approval of new medicines through different approaches, such as fast track designations, priority reviews, breakthrough therapy designation, accelerated approval, among other ¹⁰. Earlier this year, the FDA announced the establishment of an Office of Innovation to help speed drug development. Presently, the FDA is able to leverage improved understanding of biomarkers and other health technology advancements to building tools that help reduce risks and costs during the drug development process ¹¹. Likewise, emerging economies such as India and China, are also trying to speed up the approval of novel drugs and other health related medicinal products ^{12,13}.

However, regulatory changes to innovative medicine developments projects in Europe have been approached differently. The Innovation Task Force (ITF) of the European Medicine Agency (EMA) and the Offices of Innovation of the National Competent Agencies have played an important role in supporting innovation in the early phases of project developments by promoting awareness, an early dialogue between industry, researchers and the competent authority aiming to understand the regulatory requirements. The EU Medicines Agencies Network Strategy by 2020

recognizes the important role of the EMA ITF and national Offices of Innovation urging themes to seek a broader collaboration and integration across the network.

The EMA regulatory framework has specific legislation for advanced therapy medicinal product (ATMP) which are approved through a centralized procedure with a single evaluation and authorization procedure¹⁴. The certification procedure involves the scientific evaluation of quality data and when available, nonclinical data generated at any stage of product development. By following this approach, regulators can identify any potential issues early on, so that these can be addressed before submission for a marketing-authorization application (MAA). For this certification procedure, it is not mandatory to submit a complete-quality or nonclinical dossier. It is implemented as an incentive to support development of ATMP's, as an approval may be granted with on ongoing additional data ¹⁵.

In 2016, the EMA implemented an expedited regulatory pathway known as the PRIME (Priority Medicines Review Procedure) scheme to expedite approval of medicines for patients whose diseases cannot be treated or who need better treatment options to improve their quality of life without compromising patient safety. The PRIME review procedures aims to establish a proactive dialogue through scientific advice, accelerated assessment, and conditional approval between the regulatory agency and drug developers. This early dialogue facilitate the collection of robust data enabling high quality marketing authorization applications (MAAs) ¹⁶.

The Latin American context for biotechnology innovation: The Cuban experience

Low and middle-income countries like most in Latin American and the Caribbean region lack access to innovative medicines mainly as a consequence of the high-costs involved in product development, which in turn has become a threat to the sustainability of public health systems. Furthermore, the region has been undergoing a demographic ageing of societies, a factor which comes accompanied by an increased burden of chronic conditions, and therefore a demand for more complex and costly drugs ¹⁷.

The Pan-American Health Organization (PAHO) has defined that possibility or impossibility of ensuring access to medicines as one of the most tangible indicators of disparities and inequities that may exist between countries of the region, and among populations segments within the Latin American countries¹⁸. In essence, the financial determinants of access to medicines, including the price of a drug and its impact on household budgets or the financing of the health care system is becoming of considerable importance and concern across the Region ^{19,20}. Interestingly enough, Latin America has a positive outlook for innovation, despite a scarcity of resources with low indexes for research & development (R&D) activities and related investment. Some Latin American countries have invested in biopharmaceuticals and biotechnology, aimed to promote innovations and economic growth ²¹. Indeed, innovation in the region is strongly shaped by its culture, capital investment, human talent and the regulatory environment, wherein the conception of national innovation

strategies should explicitly geared link science, technology, economic and employment growth, access to medicines and affordability.

For the general public, the Cuban biotechnology industry achievements may be not known, however these achievements have been well-recognized by the international scientific community. Cuba has developed a local pharmaceutical production which covers more than 60% of the finished pharmaceutical products used in the country²². The strategy followed in Cuba has been based on a “closed loop” approach whereby drug research, development, manufacturing, clinical trials, market authorization, commercialization, and post-marketing surveillance are all coordinated by a single research organization in cooperation with other local institutions²³. Likewise, Cuba’s biotechnology is closely linked to health policies and is a key component of the country’s ability to implement universal health access and coverage. Another focus of the Cuban biotechnology industry is to generate profits from sales abroad which are plowed back into the local R&D activities and infrastructure making the industry more independent, providing the required investments to develop novel therapies, vaccines and other state-of-the art medical technologies, while positioning the products in the global market.

As part as the overall strategy of the Cuban biotechnology sector, the country in 1989 established a National Regulatory Authority, the Center for Quality Control of Medicines, Equipment and Medical Devices (CECMED), one of the first autonomous regulatory authorities in the Latin America region. The CECMED is responsible for regulating every phase involved in scientific innovation related to healthcare, that is,

from clinical trial design to post-marketing surveillance. The CECMED is also in charge to implement and over-see best practices for pharmaceuticals, equipment and medical devices, whether domestically produced and/or imported ²⁴. The CECMED throughout the years has strengthened regulatory capacities and competencies obtaining PAHO's National Reference Regulatory Authority designation since 2010. Furthermore, the CECMED was the first National Regulatory Authority in Latin America to receive the WHO certification for qualified vaccine regulation ²⁵.

It is relevant to consider that Cuba has a population of just over 11 million inhabitants, where at times, it is difficult to identify enough potential candidates to conduct large-scale clinical trials also considering that the mortality rate due to chronic non-communicable diseases is increasing. Due the aforementioned situation, the development of novel initiatives, such as the creation of the **Office of Innovation** (with the guidance and leadership of CECMED) will help to enable patients' early access to innovative medicines. These could then be integrally inserted into the drug development process together with the establishment of related policies. Cuba's biotechnology portfolio and pipeline are robust, whereby the Regulatory Authority cannot be on the sideline. On the contrary, the Cuban Regulatory Authority must be integrated through an efficient science-base, integrated, drug development process design supported by a regulated scheme able to assess the complexities of the research and development cycle with regulatory operations.

To date, global regulations and related policies require to evolve rapidly. Still, the rigid, one-size-fits-all regulatory model does not allow sufficient swift responses, with patients having to wait (at times), up to 15 years for a treatment to be approved ²⁶. Innovation is often slowed down by the significant bureaucratic hurdles required for obtaining and maintaining product registration license approvals worldwide. Therefore, strengthening the take-up of the regulatory sciences, as well as the application of multidimensional approaches, by which approval prerequisites and timelines taking into account individual products characteristics, components and health benefits should be given enough priority to build a regulatory system addressing the dilemma of flexible product introduction without compromising rigor.

If the Cuban biopharmaceutical industry is to become a respected participant in the global pharmaceutical market, the local Cuban industry must reevaluate the relationship and collaboration with the National Regulatory Agency (CECMED). This approach, in the form of a strategic collaboration and early dialogue with the Regulatory Agency will help to promote more efficient use of available resources, reducing the regulatory burden and duplication efforts, as well as, improving the regulatory submission and approval timeframes. To this effect, one of the most significant groundbreaking transformations that the CECMED is proposing through the Office of Innovation is the integration of scientific research into the regulatory framework strategy. This novel scheme will positively boost the level of domestic research and development of medicines while complying with strict regulatory requirements. Offices of Innovation work in many ways. Some offer a dedicated telephone number, with email contact or social media platform, with a dedicated

Case Officer on a 8 hour day duties, among other. The CECMED's Office of Innovation plans to align this integration with its work goals, administrative and organizational structure. Certainly, this is likely to be the least resources intensive approach, providing the necessary resources with an active approach leveraging of the quality and high technical professional skills and capacities required by the professional staff.

In a nutshell, innovation in regulation does not self-preserve. It is comprised of a process engaging internal key and strategic elements to help reach a greater impact within the regulatory ecosystem. The leading role of the Office of Innovation is a driving force of national and regional biotechnology innovation, which positively influences and promotes regulatory support at early stages of the research projects, guiding and overhauling product development strategies, more accurately, defining products and related services. In essence, modern times require changes in the conceptualization of the regulatory and scientific approaches, recognizing the contribution of Regulatory Agency regulators in the design of research and development activities. These initiatives will most certainly help improve Cuba's ability to bring innovative drugs to other globally scientific advanced markets.

Final Considerations

A key component of an innovative regulatory framework is not only how diligent it may be to help to accelerate drugs introduction to market. It is how the regulatory framework functions and its ability to develop strategic alliances between the

different players and the Regulatory Authorities, that is, embracing shared risks and establishing collaboration strategies, reaching how patients and the general population view to the likely impact scientific and technological changes. By incorporating a more collaborative approach, empowering and enhancing the access to industry and innovators to a more adequate and comprehensive system with facilitated regulatory guidance and support will certainly crucial become a cutting-edge approach facilitating the development of innovative medicines.

In the present regulatory context, due the challenge incurred by both the dynamic and complex pharmaceutical and healthcare sectors, Regulatory Agency regulators face a trade-off between the developments of strong scientific evidences of clinical effects with a consequent rapid access to market. Therefore, further transparency in the research products pipeline, in research design, its costs and a direct dialogue between regulators and innovators will generate more confidence and cost efficiency. A more dynamic collaboration will most certainly support Regulatory Agency regulators to identify emerging issues in promising healthcare and related technologies. Additionally, will be imperative for drug product innovators to understand the current regulatory landscape, so as to ensure the appropriate priority review status for approval granting in line with full regulatory oversight, in compliance with the decision-making regulatory approval process.

National Regulatory Agencies and regulatory scientists should be a reflection of leadership embracing the paradigm shift from an administrative regulation approach to a more scientific and collaborative approach. This challenge is about adopting scientific measures while redirecting current regulatory strategies of products

development, improving the flow of knowledge between drug innovators to regulatory agencies and regulatory scientific committees (and vice versa).

The recent establishment of the Office of Innovation in Cuba seeks to promote R&D initiative to help boost and improve the efficacy and productivity of the national Cuban biotechnology industry. The CECMED also seeks to align harmonization initiatives of the Cuban innovation products in line with the European innovation network and regulations so as to ensure a better alignment for new market access opportunities. To conclude, the best healthcare drug product innovators invest time and resources on to address underlying human healthcare needs. For this reason, the best regulators should actively help identify and encourage promising drug development activities (including advanced therapeutic products or combination products) to further advance the product development process towards the next appropriate level during the drug evaluation cycle with the aim to, enable faster access of innovative medicines to patients.

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Conflict of interest

The authors have declared no conflicts of interest for this article.

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