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ORIGINAL RESEARCH

The CECMED Office of Innovation: A Core Initiative to Bolster Novel Pharmaceutical Products-The Cuban Approach

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Abstract
Regulatory agencies across the Latin American region have strengthened their activities through the development of new regulatory science-based tools, standards and other approaches to evaluate and assess the safety, efficacy, quality and performance of therapeutics and devices. These processes have been implemented to promote the development and authorization of innovative new drugs and technologies, which pose a challenge to even well-established regulatory frameworks. Furthermore, in today's environment, the regulatory framework to protect public health can create barriers to marketing entry of novel drugs and medical devices. This article describes the pioneering approach that the Cuban regulatory agency (CECMED) has developed with the aim of building a comprehensive regulatory framework geared to accelerated innovation and enable successful transition of novel products from research and development to clinical practice. The Office of Innovation recently established at CECMED is the first flagship initiative of this type in Latin America and the Caribbean region. Its goal is to serve a leading role as a driving force for national and regional biopharmaceutical innovation. Herein, we discuss the conceptualization and management of the Office from the Latin American regional and national Cuban contexts.

Keywords Office of Innovation · Novel drugs · Novel therapies · Regulatory science · Latin American regulatory landscape

Introduction

Much evidence demonstrates that pharmaceutical innovation is having a positive impact on short- and long-term improvements on human health. Novel drugs and/or their combinations, vaccines against communicable and non-communicable diseases (e.g. cancer, diabetes, and orphan diseases) are being introduced at an increasingly rapid pace. Furthermore, the use of the state-of the art technologies such as nanotechnology and the application of new biomaterials are emerging [1]. The World Health Organization (WHO) has promoted the concept of health innovation to achieve universal health coverage within the context of its Sustainable Development Goals (SDGs). As part of this approach, the WHO adopted The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI) to promote a completely new approach to 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 that disproportionately affect developing countries [2].

During the early stages of development, many innovative drugs show promising evidence of activity suggesting that they could be a solution for unmet medical needs. However, the costs associated with developing these important new drugs places at risk the economic sustainability of health services and/or the out-of-pocket expenditures of individuals and families [3–5]. For the Cuban regulatory agency (Center for the State Control of Drugs and Medical Devices; CECMED), an innovative product should provide effective treatment for a specific illness with significant improvements over existing treatments or providing a verifiable therapeutic option for diseases where there is no effective treatment or in a subgroup of patients with unmet medical needs [6].

On one hand, we are clearly witnessing the emerging potential of innovative medicines, therapies and technologies to help advance population health and quality of life,

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extending life expectancy and reducing disease progression with even the probability of cures. On the other hand, regulatory gaps challenge the implementation of optimized regulatory pathways to encourage development and facilitate marketing authorization application (MAA) assessments. Moreover, improperly designed, untimely or even unnecessary clinical studies and unclear regulatory administrative requirements or expectations delay development and slow regulatory reviews creating unnecessary barriers to market entry and patients' access to new therapies [7].

It is recognized, therefore, that novel regulatory initiatives and approaches are required to stimulate innovation in order to provide the appropriate incentives for research and development activities to support innovative medicines that effectively target real therapeutic needs. This publication describes the pioneering work that is being conducted by CECMED, which is focused on building a comprehensive regulatory framework to speed innovation by integrating industry and agency expertise and regulatory capacities for translating scientific innovations into effective therapeutics. Towards meeting this goal, CECMED has established the Office of Innovation, the first of its kind in Latin America and the Caribbean region to help facilitate the exchange of expertise through an early dialogue between researchers and the Agency and support a science-based regulatory environment, thereby developing an environment conducive to national, regional and global biopharmaceutical innovation. Herein, we discuss the conceptualization and management process of this novel initiative, taking into account international, regional and national contexts.

The International Context

Health innovation is inherently linked to changes in the research environment, process improvements and optimization ultimately striving for equitable access. According to the WHO, the development of new or improved health policies, systems, products, medical devices, technologies, services and delivery methods that improve people's health adds value to the healthcare system in the form of improved efficiencies, effectiveness, quality, safety and/or affordability [2]. Health innovation can disrupt the status quo involving initiatives to address research and market failures and regulatory gaps through a holistic approach that builds new, synergistic and strategic partnerships,thereby increasing research and development competitiveness.

The global regulatory landscape has evolved into a process of regulatory diversification, influenced by the urgent need for more flexible and less burdensome regulatory requirements, without compromising the quality, efficacy and safety of innovative products. Some countries have established Innovation Offices as a first step towards implementing a comprehensive regulatory innovation pathway. Innovation Offices may go by different names, structures and functions, but they all aim to provide regulatory strategy and process clarification to those 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 opportunities have been observed in the USA, where modifications introduced to the regulatory framework have focused on accelerating the development and assessment of new medicines using a variety of flexible approaches, including the Fast Track designation, Breakthrough Therapy Designation, Priority Review, and Accelerated Approval, among others [10]. In 2019, 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, uncertainties and costs during the drug development process [11]. Likewise, emerging economies such as India and China are also trying to speed the approval of novel drugs and other health related medicinal products [12, 13].

Regulatory support for the development of innovative medicines in Europe has 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 development by promoting awareness, and supporting the early dialogue between industry, researchers and the competent authority to understand the regulatory requirements and expectations. The EU Medicines Agencies Network Strategy for 2020 recognizes the important role of the EMA ITF and national Offices of Innovation urging them to seek a broader collaboration and integration across the network.

The EMA regulatory framework has specific legislation for advanced therapy medicinal products (ATMP), which are approved through a centralized procedure with a single evaluation and authorization procedure [14]. The certification procedure involves the scientific evaluation of quality data and, when available, nonclinical data generated during any stage of product development. By following this approach, regulators can identify potential issues early on, so that these can be addressed before Marketing Authorization Application (MAA) submission. 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, and an approval may be granted with the expectation of receipt of ongoing additional data [15].

In 2016, the EMA implemented an expedited regulatory pathway known as the PRIME (Priority Medicines Review Procedure) scheme to expedite development and approval of medicines for patients whose diseases cannot be treated or who need better treatment options to improve their quality of life without compromising safety. The PRIME review procedure aims to establish a proactive dialogue through scientific advice between the regulatory agency and drug developers. This early dialogue facilitates the development of high quality MAAs, which support accelerated assessment and conditional approval that are dependent upon the collection of robust post-authorization data [16]. This approach has been designed to address multi-stakeholder expectations of innovative products from the earliest stages of conceptualization.

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, a factor that is accompanied by an increased burden of chronic conditions and therefore a demand for more complex and potentially costly innovative drugs [17].

The Pan-American Health Organization (PAHO) found inequalities in access to medicines as one of the most tangible indicators of disparities between countries of the region and among populations segments within Latin American countries [18]. 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 healthcare 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 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; consequently, national innovation strategies should explicitly link science, technology, economics, employment growth, regulatory strategies, access to medicines and affordability.

For the general public, the achievements of the local biotechnology industry may not be well known; however, these achievements have been well recognized by the international scientific community. Cuba has developed a local pharmaceutical industry that provides more than 60% of the finished pharmaceutical products used in the country [22]. 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 institutions [23]. Likewise, Cuba's biotechnology focus is closely linked to the country's health policies and is a key component of the country's ability to implement universal health access and coverage. Another goal of the Cuban biotechnology industry is to generate revenues from sales abroad, which are reinvested into local R&D activities and infrastructure making the industry more robust, 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, in 1989 Cuba established its national regulatory authority, the CECMED, one of the first autonomous regulatory authorities in the Latin American region. The CECMED is responsible for regulating every phase of scientific innovation related to healthcare, from clinical trial design to post-marketing surveillance. The CECMED is also responsible for implementing and overseeing best practices for the authorization of pharmaceuticals and medical devices, whether domestically produced and/or imported [24]. Throughout the years CECMED has strengthened its regulatory capacities and competencies obtaining PAHO's National Reference Regulatory Authority designation in 2010. Furthermore, the CECMED was the first National Regulatory Authority in Latin America to receive the WHO certification for qualified vaccine regulation [25].

Cuba has a population of just over 11 million inhabitants, where at times, it is difficult to identify enough candidates to conduct large-scale clinical trials not only for targeted unmet medical needs but also for the increasing prevalence of chronic non-communicable diseases. Therefore, the development of novel initiatives, such as the creation of the **Office of Innovation** (with the guidance and leadership of CECMED) is a key step to enable patients' early access to innovative medicines. These products can then form an integral part of the drug development process supported by the establishment of holistic healthcare and regulatory policies. Cuba's biotechnology portfolio and pipeline are robust so CECMED cannot be on the sideline. On the contrary, the Authority must be integrated through an efficient science-based, holistic, drug development process built on a regulatory scheme that is able to support and assess the complexities of the research and development cycle with integrated regulatory operations.

Global regulations and the related local policies must evolve rapidly. Therefore, the rigid, one-size-fits-all

regulatory model does not allow sufficiently swift responses, with patients having to wait (at times), up to 15 years for a treatment to be developed and approved [26]. Innovation is often slowed by the significant bureaucratic hurdles required for obtaining and maintaining product registration license approvals locally and worldwide. Therefore, strengthening the integration of regulatory sciences, as well as the application of multidimensional approaches, by which approval prerequisites and timelines take into account individual products characteristics, components and health benefits should be given enough priority to build a regulatory system that effectively addresses the dilemma of flexible product development and introduction without compromising scientific rigour.

If the Cuban biopharmaceutical industry is to become a respected participant in the global pharmaceutical market, the local Cuban industry must re-evaluate its approach, relationship and goals to collaborate with CECMED. Therefore, strategic collaboration and early dialogue with the 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 its new Office of Innovation is the integration of scientific research throughout the regulatory framework process. It is expected that this novel scheme will boost the level of domestic research and development of medicines while complying with strict global regulatory standards.

Offices of Innovation work in many ways. Some offer a dedicated telephone number with a dedicated Case Officer, an email contact or a social media platform, among others. Building on the experiences of other agencies, the Office of Innovation plans to align these approaches with its work goals, administrative and organizational structure (see Fig. 1). The Office of Innovation is integrated to CECMED institutional framework, therefore is structured and staffed in such a way that it is able to implement procedures and decision-making successfully. In operational terms, as can be seen in Fig. 1, the decision-making process focuses on a switch on–off coordination. In this approach, the executive board is called the hierarchical structure and consists of the Cuban regulatory agency director, three deputy directors, and the chief executive of the office of innovation. It needs to be emphasized, that regulatory technical representation and external experts are incorporated as appropriate. A key issue to the board is to define based on public health priority and categorization, the so-called prioritized innovative projects and/or products. This is believed to be the most resource efficient approach, providing the necessary resources with an active approach leveraging of the high quality, technical professional skills of its professional staff.

As stated earlier, Office of Innovation is planning to have a leading role in the interaction with pharmaceutical, biotechnological industry, academic institutions, and medical device companies, among others.

Innovation in regulation cannot remain stagnant. It is comprised of a process engaging key internal and external stakeholders and linking them with strategic tools to attain a

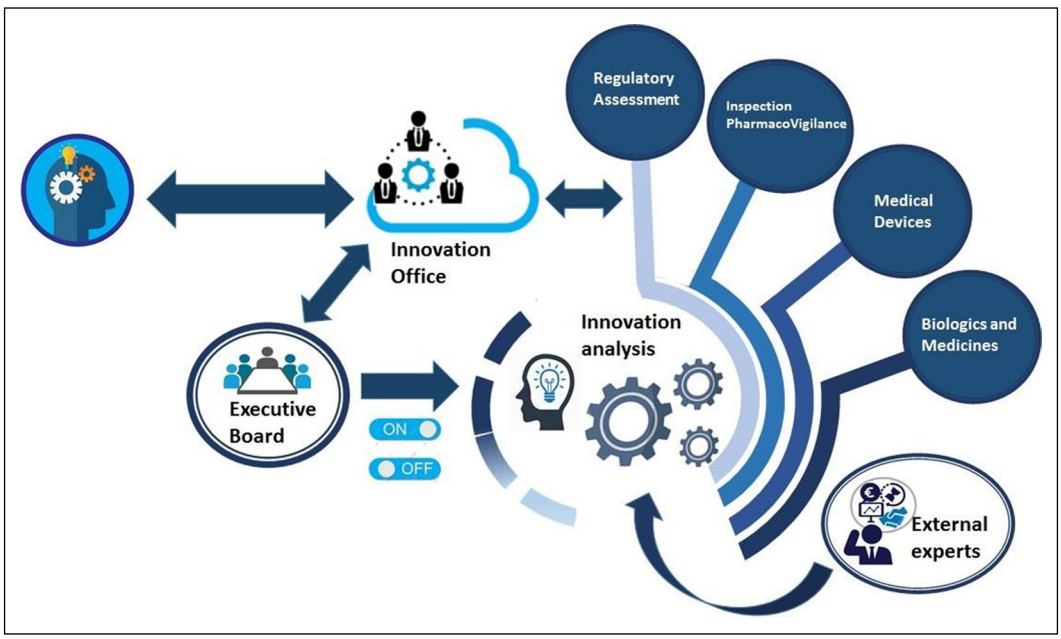

Fig. 1 Coordination Mechanism of CECMED Innovation Office.

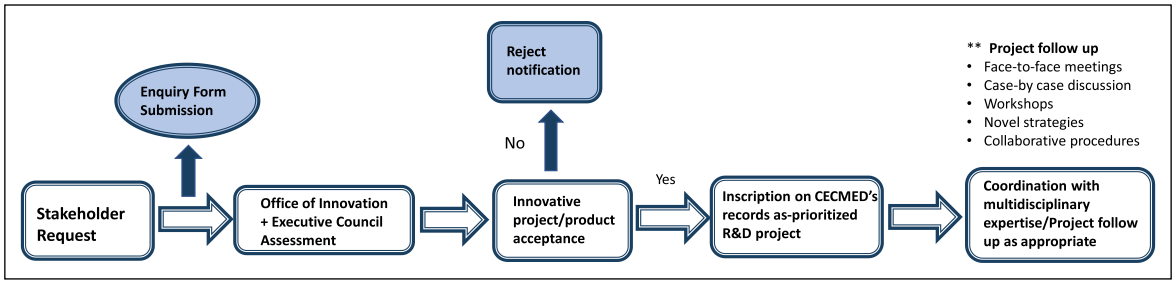

Fig. 2 General Flowchart of CECMED Office of Innovation Interaction with Stakeholders.

greater impact within the regulatory ecosystem. The Office is exchanging with experts, scientists, pharmaceutical and biotech industry from Cuba and abroad to identify opportunities and/or improvements to develop a successful model to fill the knowledge gaps and keep an iterative regulatory approach. Figure 2 shows the general flowchart developed to interact with stakeholders and to guaranty their engagement. The role of regulators is no longer as a simple observer, it is more as a collaborator acquiring knowledge regarding the regulatory and legal environment linked to the product, project or technology. Taking advantage of a proper interaction, exchange and communication channels through case-by-case discussions, face to face meetings, workshops, etc will help to clarify roles and responsibilities and to induce a constructive dialogue among regulators and stakeholders. Also, the office of innovation would help to connect a broad range of areas of expertise, look into collaborations, novel strategies and procedures that would allow CECMED to involve multidisciplinary expertise and better preparedness for clinical trials application and national license application procedures.

The leading role of the Office of Innovation is, therefore, to serve as a driving force of national and regional biotechnology innovation, which positively influences and promotes regulatory support at early stages of research projects, defining the needs for products and related services, and guiding and strengthening product development strategies. In essence, modern times require changes in science-based regulatory approaches, recognizing the contribution of regulators to the design of research and development activities. These initiatives will most certainly help improve Cuba's ability to bring innovative drugs to its patients and to meet the needs and expectations of scientifically advanced global market.

Final Considerations

Key components of an innovative regulatory framework are both how effectively it may accelerate the development and introduction of innovative drugs and how effective its ability to develop strategic alliances between the stakeholders and the regulator. This involves embracing shared risks and establishing collaborative strategies, being sensitive to how patients and the general population are likely aware of the impact of advanced scientific and technological changes. By empowering the industry and incorporating a more collaborative approach, enhancing the access by industry and innovators to a more fit-for-purpose and comprehensive system with facilitated regulatory guidance and support will become a crucial, cutting-edge approach to facilitating the development of innovative medicines.

In the present regulatory context, due to the challenges incurred by both the dynamic and complex pharmaceutical and healthcare sectors, regulators face a trade-off between the development of strong scientific evidence of clinical effects with a need for timely access to market, especially for innovative medicines. Therefore, further transparency in the research products pipeline, in research design, its costs and impact on the healthcare system supported by direct dialogue between regulators and innovators will generate confidence, clarify expectations and improve overall timeliness and cost efficiency. A more dynamic collaboration will most certainly encourage regulators to identify emerging issues in promising healthcare and related technologies. Additionally, it will be imperative for innovators to understand the changing regulatory landscape so as to ensure the appropriate facilitated development and authorization pathway is used in line with regulatory oversight and in compliance with the regulatory decision-making approval process.

National Regulatory Agencies and regulatory scientists should be a reflection of their leadership, embracing the paradigm shift from an administrative regulation approach to a more scientific and collaborative approach. The challenge is about adopting science-based approaches while redirecting current regulatory strategies for product development by improving the flow of knowledge across drug innovators, regulatory agencies and regulatory scientific committees.

The recent establishment of the Office of Innovation in Cuba seeks to promote R&D initiatives to help boost and improve the efficiency and productivity of the national Cuban biotechnology industry. The CECMED also seeks to align harmonization initiatives with the European innovation networks and the European regulations so as to ensure

a better alignment for new market access opportunities for quality Cuban biotechnology products. To conclude, the most successful innovators invest time and resources to address underlying human healthcare needs. For this reason, the most innovative regulators should actively help to identify and encourage promising drug development activities to further advance a holistic product development and regulatory process with the aim to enable faster access to innovative medicines by patients.

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Compliance with Ethics Standards

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

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