

Science at the Service of Public Health: Rafael Pérez Cristiá MD PhD General Director, Center for State Control of Medicines and Medical Devices

Conner Gorry MA

Cuba's nascent biotechnology sector began making scientific breakthroughs in the 1980s, including the isolation of human leukocyte interferon alpha (1981) and the development of the world's first safe, effective meningitis BC vaccine (1989). With positive results in hand and a growing R&D pipeline, the island nation established a national regulatory authority (NRA) to implement and oversee best practices for all pharmaceuticals and medical devices, domestically produced and imported, used in the country's universal health system. Founded in 1989, Cuba's Center for State Control of Medicines and Medical Devices (CECMED) is the entity charged with regulating all phases of scientific innovation for health, from clinical trial design to postmarketing surveillance.

Dr Rafael Pérez Cristiá, Distinguished Member of the Cuban Academy of Sciences, has been Director General of CECMED since 2000, overseeing regulation and control of unique and innovative biotechnology products and the concomitant evolution of the nation's regulatory authority. Under his guidance, CECMED has regulated unique therapies, vaccines, and pharmaceutical products—some unavailable anywhere else in the



world—aimed at improving population health both at home and abroad. Recognized internationally as one of the top 20 countries with a safe and reliable biotechnology industry and regulatory authority, Cuba is having a measurable impact on public health. In this exclusive interview, Dr Pérez Cristiá, explains how a small, resource-scarce country has rocketed into the global biotech elite—and how it intends to stay there.

MEDICC Review: Can you discuss the origins and evolution of CECMED?

Rafael Pérez Cristiá: Our biotechnology industry was born of necessity: in the early 1980s, Cuba experienced a hemorrhagic dengue epidemic followed by an outbreak of meningococcal disease, both of which led to spikes in infant mortality. Pediatric intensive care units were established in hospitals across the country to treat these diseases, but the US embargo then—as now—kept us from easily accessing medicine and technology from the USA. So it became apparent that to diagnose, treat and control disease and other health problems, we were going to have to forge our own solutions. As a result, resources were marshalled to establish scientific R&D capacities and a regulatory authority to oversee development, manufacture and distribution of vaccines and other biotechnology products. Our earliest success was VA-MENGOC-BC, the world's first vaccine against meningitis B and C, which was awarded a World Intellectual Property Organization Gold Medal in 1986. This was a milestone for us, since it was then we realized the potential of Cuban biotechnology and the impact it could have on health. But we also realized that to properly support research and development of vaccines, pharmaceuticals and therapeutics, we needed

a regulatory authority as sophisticated and trustworthy as our biotechnology industry and the products it was creating. This led to the founding of CECMED.

We reached out to international experts for training, advice and specialized know-how, launching an intense collaboration aimed at creating and designing an NRA. Although our team was small and worked from cobbled-together offices, we realized we were breaking new ground: Cuba was one of the first Latin American countries to create an autonomous regulatory authority, under the auspices of the Ministry of Public Health.

In 1992, CECMED moved to new headquarters, allowing us to expand our team and establish laboratories for independent analysis of scientific results submitted by the biotech sector. We pushed full steam ahead, instituting international standards for clinical trial design, research, development, manufacturing and surveillance, while training the necessary specialists. In 1999, our efforts paid off with another significant breakthrough: a safe and effective recombinant hepatitis B vaccine. In 2001, this vaccine received prequalification status for inclusion in the WHO's Global Alliance for Vaccine and Immunization Program (GAVI)—the first Cuban product to do so.

This was a major breakthrough for Cuban biotechnology because prequalification status requires WHO certification that the vaccine is not only safe and effective, but that it was developed, produced, tested and distributed according to international best practices. Importantly, the WHO prequalification process for a vaccine also evaluates whether the national regulatory framework meets established criteria. CECMED is re-evaluated by independent, international specialists every two years to maintain this status, which we've done since 2000. Cuba is a country with many limitations and few resources—and we haven't always made proper use of them—but our government showed the political will to create, develop and fund an internationally recognized national regulatory authority, a great source of motivation for me and others at CECMED.

MEDICC Review: Can you talk a bit more about how CECMED conceives its role?

Rafael Pérez Cristiá: The concept of Cuba's biotechnology industry is based on the principle that science should be at the service of public health—research and development of any medicine, vaccine, therapy or technology must have potential tangible benefits for improving population health. Our industry wasn't designed for profit; it was designed to resolve health problems. Guaranteeing universal access to safe, effective medicines and medical technologies—especially for the most vulnerable—is one of the most important public health strategies, recognized as such when the Millennium Development Goals were first formulated and embedded in WHO strategic plans. Through various modalities, including prioritization of R&D targeting neglected diseases, technology and knowledge transfer, and providing lower cost alternatives, Cuban biotechnology is moving closer to these goals.

All medicines used in our health system are heavily subsidized by government to guarantee access: medicines used in hospitals are dispensed free and those distributed via the national pharmacy network have extraordinarily low prices. This is a defining characteristic of our approach; I don't know of any other country with such a favorable national pricing policy for pharmaceuticals.

MEDICC Review: Can you walk us through what CECMED does and its precise functions?

Rafael Pérez Cristiá: The short answer is that CECMED, as Cuba's NRA, guarantees the safety and effectiveness of all medicines and devices used in the national health system. This includes the entire cycle of domestically manufactured products, from clinical trial design and implementation, to manufacturing, distribution, storage, and clinical application, including postmarketing surveillance of adverse events, quality control problems and the like. CECMED is also responsible for guaranteeing the safety and effectiveness of all imported medicines and technology. Independent analyses are conducted on all products, domestic and imported, at laboratories in our Havana headquarters.

CECMED must certify that all products for use in the health system conform to international best practices, which requires a large, team of inspectors, experts in various fields. In the case of clinical trials, for example, CECMED specialists evaluate and authorize trial design and protocols, provide evaluation during the four trial phases, inspect and certify trial sites, and evaluate and certify results. All these steps must conform to both scientific and

ethical international best practices before receiving CECMED certification.

Then there's the manufacturing, distribution, storage and application of new medicines, which also must meet international best practice requirements; this also falls under CECMED's purview, as does the evaluation of all medical equipment, including installation and performance once certified for use in clinical settings. Even disposable medical supplies like gloves and sutures, condoms, and products like hospital disinfectants, are evaluated by CECMED and tested in our labs. All told, there are more than 1980 products used in our national health system that have received 5-year certification and another 1000 with temporary (2-year) certification from CECMED. We've spent extraordinary amounts of time and money training the specialists needed to ensure best practices are being met, particularly since we received WHO prequalification for inclusion in GAVI. Moving forward, our biotech industry continues to make new discoveries and innovations, and so CECMED has to keep pace.

Another of our responsibilities is regulation and control of all blood products, as well as the national network of blood banks and donations, plus organ transplants, and everything involving human tissues and cells—from production and storage to recertification and surveillance. These activities are related to the international regulatory standard known as 'independent lot release.' Any licensed biological product considered high-risk—including blood products and certain vaccines—is only released for use in the health system after each lot is analyzed and certified by CECMED. This involves evaluation of all the documentation and manufacturing conditions under which it was produced, including the manufacturer's summary protocols and release certificate from the corresponding foreign NRA if applicable. After individual lots receive certification, they're released for patient use, whereupon CECMED assumes a surveillance role of these lots. Given all the certifications needed for each product and process, and the international best practices to which they must conform, it's not surprising that it takes between 12 and 15 years for a new product to progress from idea to application.

MEDICC Review: Cuba has a national program for integrative medicine. Are natural and traditional medicines evaluated by CECMED as well?

Rafael Pérez Cristiá: Promoting proven natural and alternative treatments is part of our health system's long-term development and sustainability plan. We've collaborated closely with specialists from China, Vietnam and India to incorporate complementary therapies—even yoga—into clinical practice, and medicines as well. In addition to Cuba's Basic Drug List (essential medicines used in hospitals and distributed across the country in community pharmacies), we have a Natural Products Basic Drug List. Every product on this list (153 natural medicines), whether domestically produced or imported, is evaluated and certified by CECMED and passes through the same regulatory and control processes. Some natural and traditional medicines are produced on an industrial scale; those manufactured locally are tested at municipal and provincial laboratories that are inspected and certified by CECMED—again applying all relevant international best practices—before they are sent to CECMED's lab for safety and effectiveness analysis. This certified network of local laboratories, staffed by specialists, means natural products—including, for example, cough

syrups, propolis and other apiary-derived medicines—can be distributed to pharmacies and dispensed to the public safely and efficiently.

MEDICC Review: You mention collaboration with several countries. Can you elaborate on the international component of CECMED's work?

Rafael Pérez Cristiá: In recent decades, and especially given the increasing global health burden of chronic disease, pharmaceutical and biotech industries have evolved exponentially. This has permitted the production and marketing of medicines that are safer and more effective thanks to advanced technology, manufacturing and other best practices, strict surveillance and controlled protocols. This has been fundamental in the fight against certain complex diseases, but the regulatory authority certifying these medicines must be fully integrated into the international arena if such medicines are going to reach the people who need them.

CECMED and our regulatory framework are designed to guarantee that products conform to established protocols and quality standards. Once products are certified for patient use, CECMED conducts regular surveillance to ensure they are safe and effective, and address the health problem for which they were designed and approved. Of the 761 medicines on Cuba's 2018 Basic Drug List, 273 are imported, as are 95% of all disposable and consumable medical supplies. All these products are subject to the same regulation and control for use in our health system.

We have strong, time-tested relationships with international and country NRAs, allowing us to play a dynamic role in providing access to these medicines to people around the world. Cuba currently exports pharmaceuticals and biologicals to over 50 countries, and has bilateral technology transfer agreements with many, including China, Russia and Brazil. In the latter case, technology transfer and training of local specialists allows Brazilian manufacturing facilities to produce Cuban products like recombinant human erythropoietin (developed by the Molecular Immunology Center, CIM) with the same quality, safety and effectiveness guarantee as if it were produced here, but at more affordable prices for Brazilians since it is manufactured domestically. Nevertheless, for this technology transfer to work, to assure all the necessary guarantees of safety and effectiveness, our separate NRAs needed to be on the same page, so to speak. So we developed a bilateral Regulatory Technical Committee—the first joint regulatory authority initiative of its kind in Latin America—to ensure biological standardization of Brazilian-manufactured erythropoietin.

CECMED is leaving its imprint on a global scale as well. In 2000, it was the first NRA in Latin America to receive WHO certification as qualified for vaccine regulation. This led to the aforementioned prequalification status for Cuban recombinant hepatitis B vaccine for GAVI; there are two additional Cuban vaccines with prequalification status – a *Haemophilus influenzae* type b (Hib) vaccine and the meningitis ACW-135 vaccine, developed collaboratively with Brazil. Furthermore, CECMED's Quality Management System has been certified by the Spanish Association for Standardization and Certification (AENOR), an IQnet member for the past 10 years, a certification recognized in 25 countries, including the USA and Canada; again, we were one of the first regulatory authorities in Latin America to receive this distinction.

In 2010, CECMED was certified as a PAHO Regional Reference Regulatory Authority for Medicines and Biologicals; we received Level 4 status, the highest certification. CECMED was recertified in 2016 at this level by international experts and will be re-evaluated in 2019. In 2016, CECMED also achieved observer status in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; only two other countries in Latin America, Colombia and Mexico, share this status; Brazil is an active member. After three years in this observer role, CECMED is eligible to become an active member, requiring a rigorous review and evaluation process. Recognition by these organizations and entities—the gold standards of medicine and medical equipment regulation and control—places us in the global 'big leagues.' Several leading Cuban products are now generating considerable interest abroad, including Heberprot-P (for treatment of diabetic foot ulcer; Genetic Engineering and Biotechnology Center); CIMAvax-EGF (for non-small cell lung cancer; CIM); cancer-fighting monoclonal antibodies; and several biosimilars.

MEDICC Review: Being a small, developing country in the global 'big leagues' must come with its attendant problems. What is the biggest challenge for CECMED in the current international context?

Rafael Pérez Cristiá: One challenge we face is precisely because of our small size: with a population of just over 11 million people, it can be difficult to conduct large-scale clinical trials. Sometimes it's simply impossible to identify enough potential candidates. In these cases, we conduct multicenter trials or look for candidates outside of Cuba. These multicenter/international trials are subjected to all the necessary scientific and ethical norms, and several trials of this type are ongoing.

However, in my opinion, the greatest challenge to all NRAs not only CECMED, is where scientific innovation intersects with the administration of regulation and control. We need to change the paradigm. The speed and sophistication with which new discoveries are emerging—we're talking about a diversity of high-quality products with the potential to transform health—are outstripping the capacity of regulatory authorities to respond. Today, we're close to making major breakthroughs in the early stages of a product's development, alternatives that hold the possibility of benefitting patients, but the rigid, one-size-fits-all regulatory model means patients have to wait up to 15 years for a treatment to be approved. And of course, some can't wait. This poses the question of how to introduce flexibility without compromising rigor. To do this, the regulatory process has to be directly linked to regulatory science, with approval prerequisites and timelines taking into consideration each product's components, characteristics and possible health benefits.

This is only possible if regulatory scientists have the same level of scientific knowledge and application of best practices as the researchers making the discovery. If there isn't parity between the scientists making discoveries and the specialists evaluating and certifying their discoveries, there are going to be lengthy delays before product approval. Cuba's biotechnology portfolio and pipeline are robust, with many products and projects; as a regulatory authority, we can't be on the sidelines. To be able to respond to this demand, we have to be integrally and seamlessly inserted into the development process and policies, without compromising our integrity. 