

Regulatory evolution and challenges from the perspective of public laboratories vaccine producers in Brazil

A evolução regulatória e os desafios na perspectiva dos laboratórios públicos produtores de vacinas no Brasil

La evolución regulatoria y los desafíos desde la perspectiva de los laboratorios públicos productores de vacunas en Brasil

Monique Collaço de Moraes Stávale ¹
Maria da Luz Fernandes Leal ¹
Marcos da Silva Freire ¹

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Abstract

The regulation of biological products has evolved rapidly in recent years due to quality issues impacting people's lives and the advent of new technologies, with constant changes in regulations that dictate how a product is registered, produced, and monitored. In the case of vaccines, the responsibility of regulators and manufacturers in guaranteeing quality, safety, and efficacy is even more critical, since vaccines are mostly used in children and healthy patients. In this scenario, manufacturers need to create strategies to keep their products and installations adequate and up-to-date with a fully operational quality system. Meanwhile, regulatory agencies have the role of guaranteeing that products meet the established criteria without compromising the supply of medicines to the population.

Vaccines; Health Authorities; Formal Social Control

Correspondence

M. C. M. Stávale
Instituto de Tecnologia em Imunobiológicos, Fundação Oswaldo Cruz.
Av. Brasil 4365, Rio de Janeiro, RJ 21040-900, Brasil.
monique.moraes@bio.fiocruz.br

¹ Instituto de Tecnologia em Imunobiológicos, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.



Introduction

The direct and indirect benefits of immunization are undeniable, with a considerable reduction in mortality and a decrease in the number of hospitalizations due to preventable diseases. Vaccines have thus played a unique historical role in public health, confirming that prevention is better than treating ¹.

The first records of the use of vaccines introducing attenuated versions of the virus into the human body date to 10th-century in China in the fight against smallpox, when scabs from patients' sores were crushed and the powder was blown on people's faces ².

However, the term "vaccine" appeared in 1798 following an experiment by Edward Jenner, an English physician and scientist. Jenner had heard reports of farmworkers who did not catch smallpox because they had already had cowpox, which has a milder impact on the human body ³. In 1881, when French scientist Louis Pasteur began to develop the second generation of vaccines to prevent fowl cholera and carbuncle, he suggested the term "vaccine" (from the Latin *vaccinus*, meaning of or from the cow) to baptize his recently created substance, as a tribute to Jenner ⁴. Mass production of vaccines began from that point on, and vaccines became essential in the fight against diseases. With the increasing volumes and expansion of vaccines' use worldwide, the problems and adverse events gained greater visibility, caused by quality issues and the lack of clinical evidence for the vaccines used at the time.

The importance of independent assessment of drug products before launching them on the market has been perceived at different moments and in different regions of the world. In many cases, such assessment has been motivated by tragedies, such as the case of the horse named

"Jim" in 1901. A large share of the serum collected from Jim was administered to children with diphtheria, and 13 children contracted tetanus from Jim's blood and died. An investigation showed that no control tests had been performed on the serum batches. The incident led to the concept of adulteration in the regulation of biologics, and the U.S. Congress passed the Biologics Control Act in 1902 ⁵. The law set a new course for federal public health policy and paved the way for a new wave of consumer protection laws for foods, drugs, cosmetics, and other products. From then on, vaccines, sera, toxins, and biological medicines began to be regulated by the U.S. Federal Government to control their trade and ensure safe, pure, and properly labeled products. This required annual licensing of manufacturers to produce and sell vaccines, sera, and antitoxins ⁶.

Drug manufacturers were required to undergo inspections, and licenses could be revoked or suspended when necessary. Drug manufacturing had to be supervised by a qualified scientist. The products had to be labeled with the name, expiration date, and manufacturer's address and license number ⁶.

The U.S. Congress also created an agency to enforce the law, the Center for Biologics Evaluation and Research of the Food and Drug Administration (FDA).

Even after these measures were implemented, in 1955 vaccines experienced another sad episode, the "Cutter incident". In this tragedy, the production of inactivated polio vaccine by Cutter laboratories in its industrial installations resulted in the vaccination of two hundred thousand persons with a virulent strain of poliomyelitis. This was one of the worst disasters in the history of vaccination: 70,000 people contracted poliomyelitis, two hundred suffered permanent paralysis, and ten died. The Cutter incident left a legacy for health regulation, since it forced the federal regulation of vaccines, which now enjoy safety assessment unequalled by any other medical product ⁶.

The court ruling that held Cutter liable for payment of damages opened a precedent for a series of lawsuits. As a result, vaccines were the first medical products that were nearly absent from lawsuits. In this scenario, in 1986 the National Vaccine Injury Compensation Program was introduced in the United States to protect vaccine manufacturers from lawsuits. Even so, many pharmaceutical companies opted to abandon the vaccines field altogether ⁷.

Starting in 1962, U.S. manufacturers began to submit "substantial evidence" of the efficacy and safety of products for the market. Other countries, regardless of whether they had initiated previous registration controls on products, witnessed a rapid increase in the 1960s and 1970s in laws, regulations, and guidelines to report and assess data on the safety, quality, and efficacy of new drugs ⁸.

The pharmaceutical industry was becoming more international and pursuing new global markets, but discrepancy was so great in technical requirements from one country to another that the industry found it necessary to duplicate many procedures and tests (both time-consuming and costly) in order to market new products internationally. Europe proceeded with the development of a single market for pharmaceutical products, and the success achieved in Europe proved that harmonization was feasible⁹.

Discussions were thus launched in Europe, Japan, and the United States on possibilities for harmonization, and action plans began to materialize in the World Health Organization International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989. Shortly afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint initiative by the regulatory sector on international harmonization. The International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use (ICH) was created in this context¹⁰.

The ICH convenes regulatory authorities and the pharmaceutical industry to discuss scientific and technical drug registration issues. Since it was created, the ICH has evolved gradually with the mission of achieving greater international harmonization to guarantee that safe, effective, and high-quality drug are developed and registered efficiently in terms of resources¹⁰.

In Brazil, the control of drugs, foods, vaccines, and other health products was done inconsistently, with the analyses performed by the Central Laboratory for the Control of Drugs, Medicines, and Foods (LCCDMA, in Portuguese)¹¹.

On September 23, 1976, Brazil finally created a legal health framework for drugs with the enactment of *Law n. 6,360*¹² and *Decree n. 79,094*¹³, published on January 5, 1977. Under *Law n. 6,360*, establishments responsible for manufacturing, importing, storing, and distributing medicines, among other functions, had to be authorized by the Brazilian Ministry of Health to begin conducting these activities.

The Brazilian National Health Surveillance Agency (Anvisa) was not created until January 26, 1999, under *Law n. 9,782*¹⁴, with the mission of promoting and protecting the population's health through health control of the production and consumption of products and services subject to health surveillance, including the related environments, processes, inputs, and technologies.

Anvisa was thus structured to meet the needs of society and the market and launched the process of developing the country's health regulatory framework, which now consists of hundreds of documents. The qualification process for the pharmaceutical market that began with the creation of Anvisa became a constant process. Since then, in order for manufacturers to obtain marketing authorization to distribute and market drugs in Brazil, they must submit to legal procedures that basically involve authorizations and operating licenses, the marketing authorization process that assesses data on production, quality, safety, and efficacy, and a local manufacturing site inspection stage, when conditions of good manufacturing practices (GMP) are assessed¹⁵.

With the exception of the legalization itself, in which there were no significant changes over time, the other elements comprising the stages that manufacturers must complete before making their products available have undergone significant changes since the creation of Anvisa and publication of the regulatory framework.

Health regulation for marketing authorization of biological products

In relation to the regulation of information to submit together with an application for registration, although Anvisa was created in 1999, the first regulatory framework for biological products was only published in 1994 under *Ruling n. 107*. On the occasion, the National Institute for Quality Control in Health, Oswaldo Cruz Foundation (INCQS/Fiocruz) became one of the arms of the Health Surveillance Secretariat of the Brazilian Ministry of Health in the implementation of the National Health Policy¹⁶.

In 2002, biological products received their first regulation by Anvisa under *RDC n. 80/2002*¹⁷. The Resolution made a distinction between biological products that “*contain a molecule with known biological activity*” and those which “*contain a molecule with new biological activity and enjoy patent protection*”, the

latter assigned to new biological products in the country. *RDC n. 80/2002* required the submission of simple information on production and quality control. Exceptionally, the manufacturer could request of Anvisa the substitution of clinical trials (phases II and III) with other documents proving clinical safety and efficacy.

To resolve the liability of products already on the market, Anvisa separated biological products into three groups according to the period in which the marketing authorization application had been filed. Products that were under review when *RDC n. 80/2002* was issued would have a year to adjust, those already registered would have two years, and new applications would have to comply with the new format immediately, with the submission itself¹⁷.

Relatively quickly, three years the first regulation was issued, a new framework for registration of biological products was established in 2005 under *RDC n. 315/2005*¹⁸. This resolution was more rigorous than the previous one, and information on the description of the manufacturing process, validation of the transportation chain, and clinical studies on the non-inferiority of non-new biological products became mandatory. Although *RDC n. 315/2005* was more rigorous, it did not orient manufacturers on the different categories of biological products.

In 2010, Anvisa issued *RDC n. 55/2010*¹⁹, establishing a new regulatory framework and new definitions of biological products and new biological products: “*XV - Biological Product: is a biological drug not new or known that contains a molecule with known biological activity, already registered in Brazil and that has gone through all stages of manufacture (formulation, filling, lyophilization, labeling, packaging, storage, quality control batch release).* (...) *XX - New Biological Product: is the biological drug that contains a molecule with known biological activity, not previously registered in Brazil and which has completed all the manufacturing stages (formulation, filling, lyophilization, labeling, packaging, storage, quality control, and batch release)*”.

This resolution also created the need for immunogenicity studies and pharmacovigilance and risk mitigation plans. Another novelty in the new RDC in relation to the previous resolutions was the specific recommendations on different types of biologics, whereby vaccines, blood products, and biotechnological products were subject to different requirements. *RDC n. 55/2010* was thus a step forward in regulation and aligned Brazil with international regulatory practices.

Another stride in the regulation of biologics was *RDC n. 49/2011*²⁰, related to post-registration variations, since such requirements had previously been treated within the regulation for the marketing authorization of biologics. *RDC n. 49/2011* classified the alterations in three levels according to complexity: level 1 does not require prior approval by Anvisa for implementation, while levels 2 and 3 can only be implemented after the agency's approval.

Health regulation of good manufacturing practices

In addition to efficacy, safety, and access, quality is one of the four pillars of drug manufacturing established by World Health Organization (WHO) as indispensable for any health product. An important milestone in GMP requirements was the 28th World Health Assembly held by the WHO in May 1975, which approved the Good Manufacturing Practice Guideline for Pharmaceutical Products, which in turn provided the basis for Brazil's *Ruling n. 16/SVS/MS* on March 6, 1995, issued by the Health Surveillance Secretariat. That provided the Brazilian pharmaceutical industry with a domestic version of GMP requirements^{21,22}.

The creation of Anvisa in 1999 gave the sector a new regulatory dynamic, in which the Agency acted on various health services and products through a well-defined regulatory environment associated with inspection¹⁵.

Anvisa thus published the first regulation for GMPs for pharmaceutical products, *RDC n. 134/2001*²³. The resolution considered the WHO guidelines on quality certification of pharmaceutical products, standardized health surveillance activities, and clearly determined the Agency's inspection role in the verification of GMPs through the establishment of inspection routines. Most of the items proposed by *RDC n. 134/2001* was for immediate implementation, with some exceptions, during which the manufacturers would have an 18-month timeframe. The exceptions with a longer deadline for implementation included the validation of aseptic filling of sterile products, installation of the lyophilizer in the aseptic filling area, and validation of the analytical methodology.

In 2003, Anvisa replaced *RDC n. 134/2001* with *RDC n. 210/2003*²⁴, with the novelty that the resolution established the classification and criteria for the assessment of the items described in the inspection routine for drug manufacturers based on the inherent potential quality and safety risk in the manufacturing process, besides confirming mandatory validation of analytical methods.

*RDC n. 17/2010*²⁵ replaced *RDC n. 210/2003* and introduced a series of changes with impact on the pharmaceutical industry, especially for manufacturers of sterile products. *RDC n. 17/2010* created the need for validation of online systems and the investigation of out of specification findings during quality control, besides including items pertaining to water for pharmaceutical use, which until then lacked an appropriate regulation.

In addition, two critical changes led to production stoppages in public laboratories with consequences for the supply of vaccines to Brazil's National Immunization Program (PNI). One change was the restriction on sharing areas, and the other was in the grades of clean areas used for drug manufacturing. Manufacturers were previously required to produce in grade A surrounded by grade C, and were now required to produce in grade A surrounded by grade B. This adjustment required manufacturers to shut down their installations for retrofitting and implementation of new air conditioning systems. Some public manufacturers experienced long periods with their installations non-operational, thus compromising the supply of vaccines to the PNI.

In August 2019, Anvisa published *RDC n. 301/2019*²⁶. This version of GMPs has a different format from that of the previous versions, since only the common aspects of the pharmaceutical quality system were published in the RDC format. The specific rules, such as for sterile products, biologics, and systems validation were published in the Standard Instruction format. The new format aims to lend greater flexibility and speed to updating the GMP requirements, since the regulatory flow for changing a Standard Instruction is simpler than the flow for an RDC. While the previous RDC was based on the WHO Guideline of 2003, the current resolution follows the Pharmaceutical Inspection Cooperation Scheme (PIC/S), since the Agency is in a process of adherence to the system of cooperation among regulatory agencies in the field of GMPs. As for technical aspects, the new regulation increased the rigor in the elements comprising the pharmaceutical quality system and the need for involvement and commitment from the top management, reflecting its alignment with the international guidelines. There is also greater detail in the requirements, which helps companies implement them.

Sharing of areas is allowed again, as long as the company proves by means of risk analysis tools and validation of cleaning that the removal of residues from previous production was conducted effectively and that it does not pose the risk of cross-contamination and to the toxicological analysis of the products processed there. If, on the one hand, the standard proves more flexible in the requirements applicable to installations and processes, on the other, management tools are subject to greater weight and accountability, creating the need for companies to establish a robust risk management process²⁶.

RDC n. 301/2019 has a broader scope, since its *Standard Instruction n. 45*²⁷ provides guidelines for GMPs for experimental drugs.

In relation to the timeframe for implementation, *RDC n. 301/2019* entered into force 45 days after its publication, with the exception of some items, for which a longer deadline was granted for implementation. An example is the establishment of a quality risk management process that includes toxicological and potency assessment to assess and control the risks of cross-contamination in the manufactured products. In this case, the implementation can be conducted gradually, beginning with structuring and training, where the deadline is six months, until total compliance covering 100% of the portfolio, where the company has 48 months to implement the requirement²⁶.

Health regulation for clinical research

As with GMPs and information on a drug's production and quality control, safety and efficacy data are essential parts of the regulatory package assessed by Anvisa for granting a marketing authorization.

However, clinical research involves two major assessments: an ethical assessment, which considers whether the proposed protocol complies with national and international regulations for conducting research in human subjects, safeguarding the safety and well-being of research participants, and a technical and regulatory assessment focused on health issues.

Since the current article addresses technical health aspects, it focuses on the evolution of requirements by Anvisa in assessments and approvals of clinical trials in Brazil.

As occurred with other components of registration, health regulation for clinical research has evolved gradually. Before Anvisa's creation, the document that specified the requirements for clinical research in Brazil was *Ruling n. 911*²⁸ of November 12, 1998. This was a document published by the Health Surveillance Secretariat with a simple text listing 11 documents to be submitted with applications for authorizations to conduct clinical research with new drugs, medicines, vaccines, and diagnostic tests. Despite the document's superficiality, the ethical issues were preserved, since the list of requirements included the need to prove that the study site's Institutional Review Board (IRB) is registered with and approved by the National Commission for Research Ethics (CONEP), together with the review by the IRB approving the clinical protocol and free and informed consent form²⁹.

Following the creation of Anvisa, the first regulation on clinical research issued by Anvisa was *RDC n. 219/2004*²⁹, establishing the rules for elaborating the dossier to obtain the Special Communiqué for conducting clinical research with drugs and other health products. *RDC n. 219/2004* included the need for greater detail in the documents submitted in the application for clinical research and authorized Anvisa to conduct audits to verify the degree of adherence to good clinical practices and to the prevailing Brazilian legislation.

The above-mentioned resolution was criticized for having determined that multicenter trials would be required to request a Special Communiqué for each participating study site, which causes delay in the approval of clinical trials³⁰.

In June 2008, Anvisa issued *RDC n. 39/2008*³¹, which became the prevailing regulatory framework. *RDC n. 39/2008* aimed to align the Brazilian regulation with international standards, since it allowed trials that had been analyzed and approved in countries with reference regulatory agencies to receive simplified review. The following agencies were considered references: FDA – USA; European Medicine Agency (EMA) – European Union; Pharmaceutical and Medical Advice Agency (PMDA) – Japan; and Health Canada – Canada.

Beginning with *RDC n. 39/2008*, all phase I, II, III, and IV trials had to present proof of the clinical trial's registration in the Brazilian Clinical Trials Registry (ReBEC, in Portuguese), or proof of submission. Cases prior to the new resolution were allowed to submit proof of the trials' registration in the International Clinical Trials Registration Platform (ICTRP)³².

Another positive point in *RDC n. 39/2008* was the simultaneous review of all the study sites, issuing a single Special Communiqué per trial, making the trial's approval relatively quicker.

The currently prevailing regulatory framework for clinical research is *RDC n. 9/2015*³², issued on February 20, 2015, replacing *RDC n. 39/2008*, introducing the concept of Clinical Drug Development Dossier (DDCM, in Portuguese) and Specific Clinical Trial Dossier. While the latter features the information for each trial, such as the study protocol and proof of registration in the database, the DDCM consists of a set of information and documents on all stages of the product's development up to the moment of submission. Reconfirming Anvisa's commitment to research development in Brazil and with the understanding that overly lengthy review processes compromise the Agency's national and international credibility, *RDC n. 9/2015* aimed to establish more streamlined review strategies, without compromising the trials' technical quality.

Discussion

Anvisa is known today as a strong regulatory agency that plays an important role in strengthening the Brazilian pharmaceutical industry. Products registered in Brazil are considered safe and with guaranteed quality. The evolution of the Agency's inspection process is visible. It started from an assessment based on check items (check list) in 2003, through *RDC n. 134/2003*, and reached, in 2019, one inspection based on risks, in which the quality system is evaluated in a systemic way.

This evolution was necessary for the enhancement of the Brazilian pharmaceutical industry and to achieve the currently demanded quality standards. However, the onus was that various laboratories were shut down, and important drugs were discontinued. The scenario was no different in the public laboratories, with an increase in the degree of requirements, which partly involved retrofits, alongside

budget constraints and bureaucratic procedures. Some laboratories had to shut down their production temporarily and, in some cases, even permanently.

Anvisa maintained its strategy of regulatory convergence, joining the PIC/S and basing its new regulatory framework (*RDC n. 301/2019*) on the set of guidelines of the principal international regulatory agencies.

The new RDC is consistent with previous discussions between Anvisa and the various stakeholders. The resolution reconfirmed the strengthening of the concept of pharmaceutical quality system rather than quality guarantee, consolidating risk management tools and the approach throughout the product's life cycle.

The fact that the new RDC does not include requirements involving complex structural issues (unlike the previous resolutions) does not make the provisions any less challenging for the public laboratories to implement adjustments, since the changes involve culture this time. The new requirements are data integrity, risk management, and a strong quality management system, which require manufacturers to invest in training their personnel.

Sharing areas is allowed again, based on risk assessment and adjustment to the processes of validation and toxicological analysis. This is an important issue, because in the past, with *RDC n. 17/2010*, such sharing had been prohibited. Pharmaceutical companies, even with their processes validated and qualified, had to choose which of their products would be maintained and which would be eliminated from their portfolio. *RDC n. 17/2010* had been based on the WHO guideline, which allowed sharing in special cases, and in practice the *RDC n. 17/2010* interpreted such cases as public calamities. This point had huge impact on public laboratories. In Immunobiological Technology Institute – Bio-Manguinhos, Oswaldo Cruz Foundation, the option was to interrupt the production of meningococcal AC polysaccharide vaccine in order to maintain yellow fever vaccine, since attenuated live virus vaccines and subunit or inactivated vaccines could not be filled on the same line, even for campaign production.

Although the new resolution provides for shared areas, the criteria are still being discussed, since investments will be needed again in training personnel. This time, it will be essential to have toxicologists with experience in cleaning validation.

As for the product registration phase, as with GMPs, the resolution pertaining to marketing authorization of biological products also merits revision. Importantly, the regulation that addresses marketing authorization of biological products, *RDC n. 55/2010*, was issued in 2010. Since we are now in 2020, we have had 10 years of new developments in biotechnology that may not be covered by a regulation, generating delay in the Agency's response time.

Drugs obtained from transgenic animals and plant platforms are examples that still lack specific guidelines. The lack of a regulatory document with guidelines for some technologies produces uncertainties for the manufacturer, since the registration is analyzed case by case.

There are some incipient initiatives by the Agency for collaboration with universities in drafting and updating regulatory requirements. Strengthening this partnership should lead to important gains in Anvisa's response time to new technologies and the development of science-based regulation.

Anvisa bases its work on the precautionary principle, that is, given a new situation or technology, the Agency's position will be as conservative as possible to guarantee the population's safety and to confirm its role as health regulator.

Anvisa has adopted some strategies to concentrate efforts and time on products with the highest risk. In March 2019, the Agency published *Public Consultation n. 633*, which determines the minimum requirements for registration of biological products involving lower complexity.

Anvisa also aims at alignment with international regulatory practices for product marketing authorization. In November 2016, when the Agency joined the ICH, it joined 18 working groups that discuss new requirements and updating of existing requirements on topics covered by the ICH.

As an ICH member, Anvisa committed to an action plan implementing five guidelines in five years and approximately 60 guidelines in a timeframe to be determined, in addition to guidelines with immediate implementations.

One of the guidelines for implementation in five years is the Common Technical Document (CTD), which addresses the format and content for the documents submitted to the Agency for mar-

keting authorization. Many countries adopt this format, the objective of which is have a single dossier to be applied to different regulatory agencies, avoiding rework by manufacturers and thus allowing more rapid availability of promising products. Unfortunately, in practice there are local specificities, and the goal of a single marketing authorization document has still not been achieved. However, since Anvisa is part of this group, Brazil will be monitoring this evolution closely.

Conclusion

In the past, progress of regulation was motivated by tragedies and quality issues. At present, new technologies and more sensitive methodologies motivate the regulatory agencies to issue new requirements. However, when publishing new requirements, the agencies should conduct a detailed assessment to determine whether the new requirement actually adds value to quality, safety, and efficacy, in order for the requirement not to become a barrier that ends up shutting down various manufacturers, especially in developing countries, jeopardizing the supply of vaccines that have already been proven to immunize entire populations.

Public laboratories experience this challenge on a daily basis. On the one hand, Brazil has a widely acknowledged regulatory agency that has gone international through participation in forums that discuss the directions of global pharmaceutical regulation, such as PIC/S and ICH. On the other hand, these same laboratories need to deal with the restrictions applied to public agencies, where the timeframes required for retrofits and implementation of requirements are not always in step with the regulatory changes. The recently published *RDC n. 301/2019* introduces some changes in this scenario. In the past, updates to the regulatory standard produced major impacts on infrastructure works and installations. This time, a strong quality system and the commitment by top management become the central point of the discussion. However, this change does not reduce the challenges for public laboratories, which not only have to update their industrial installations but also invest in the management capacity-building and modernization.

Contributors

M. C. M. Stávale collaborated in the literature review and writing of the manuscript. M. L. F. Leal contributed in the article's conception and design, data analysis and interpretation and review of the article. M. S. Freire collaborated in the critical revision of the article's intellectual content.

Additional informations

ORCID: Monique Collaço de Moraes Stávale (0000-0001-7051-8233); Maria da Luz Fernandes Leal (0000-0002-8886-8116); Marcos da Silva Freire (0000-0002-4723-8994).

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Resumo

A regulamentação para produtos biológicos vem evoluindo rapidamente ao longo dos últimos anos, seja motivada por questões de qualidade com impacto na vida das pessoas, seja pelo advento de novas tecnologias. As mudanças nas regulamentações que ditam como um produto deve ser registrado, produzido e monitorado são constantes. A responsabilidade de reguladores e fabricantes na garantia da qualidade, segurança e eficácia das vacinas torna-se ainda mais crítica, uma vez que essas substâncias são utilizadas, em sua maioria, em crianças e em pacientes saudáveis. Diante desse cenário, fabricantes precisam criar estratégias para manter seus produtos e instalações adequadas e um sistema da qualidade atualizado e operante. Por outro lado, as agências reguladoras têm o papel de garantir que os produtos que estão em uso atendam aos critérios estabelecidos, sem comprometer o fornecimento de medicamentos para a população.

Vacinas; Autoridades de Saúde; Controle Social Formal

Resumen

La regulación para productos biológicos ha evolucionado rápidamente a lo largo de los últimos años, sea motivada por cuestiones de calidad con impacto en la vida de las personas, o por el advenimiento de nuevas tecnologías. Los cambios en las regulaciones que dictan como un producto debe ser registrado, producido y monitoreado son constantes. La responsabilidad de reguladores y fabricantes en la garantía de la calidad, seguridad y eficacia de las vacunas se convierte en algo todavía más crítico, ya que estas sustancias se utilizan, en su mayoría, en niños y pacientes saludables. Ante este escenario, los fabricantes necesitan crear estrategias para mantener sus productos e instalaciones de forma adecuada, además de un sistema de calidad actualizado y operativo. Por otro lado, las agencias reguladoras tienen el papel de garantizar que los productos que están en uso atiendan a los criterios establecidos, sin comprometer el suministro de medicamentos para la población.

Vacunas; Autoridades de Salud; Control Social Formal

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