

## Incorporation and use of medicines in the Brazilian Unified National Health System: changes and risks of new Ministry of Health legislation

Incorporação e uso de medicamentos no Sistema Único de Saúde: mudanças e riscos com os novos atos normativos do Ministério da Saúde

Incorporación y uso de medicamentos en el Sistema Único de Salud: cambios y riesgos con los nuevos actos normativos del Ministerio de Salud

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In the last 15 years, Brazil has experienced a progressive institutionalization of health technology assessment (HTA), especially within the public system. The Brazilian National Policy on Health Technology Management assigns to the HTA the role of generating scientific evidence to support decision-making entities regarding the incorporation and monitoring of the use of technologies in the health system, in addition to guiding health professionals and users <sup>1</sup>.

However, the process of using HTA in decisions related to health technologies within the Brazilian Unified National Health System (SUS) had a slow implementation and only became fully effective with the Department of Science, and Technology (DECIT) and the Science, Technology, Innovation and Strategic Health Supplies Secretariat (SCTIE), in 2000 and 2003, respectively. The emphasis that was once aimed at selecting the essential medicines for the SUS – as part of the National Medicines Policy agenda – gradually started losing ground in favor of HTA and incorporation. In January 2006, the Brazilian Ministry of Health created the Technology Incorporation Commission (CITEC), for technical counseling on the analysis of new technologies <sup>2</sup>.

Another important milestone in this institutionalization process was the creation of the National Committee for Health Technologies Incorporation (CONITEC), via the publication of *Law n. 12,401* of April 2011 <sup>3</sup>.

CONITEC advises the Brazilian Ministry of Health in decisions regarding the incorporation, exclusion, or alteration of medicines, products, and procedures in SUS <sup>1</sup>. Its creation strengthened the relationship between HTA and the development of a policy based on scientific evidence regarding the efficacy, safety, accuracy, and effectiveness of health technologies, as well as the development of economic studies aimed at the efficient application of resources and at the economic and financial impact of their introduction and use. The regulatory frameworks that guide the incorporation process defined flows, criteria, and deadlines for the evaluation and incorporation of technologies, promoting an expansion of society participation, via consultations, public hearings, surveys, dissemination of reports, and patient involvement to inform the decision process.

However, the political and non-technical conduct regarding the incorporation outcomes of such policies exposes difficulties <sup>4</sup>. There are still problems in CONITEC analysis and judgment processes, such as heterogeneity of the reports, some of which are quite simplified and without clearly arranged justifications for the recommendations; lack of standardization of analytical methods; and non-compliance with requirements contained in the internal regulations on the type and quality of evidence

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to be considered. Furthermore, there is a need for greater transparency and inclusive involvement of the various social segments concerned and actions that are more proactive, independent, and not exclusively driven by demands, in addition to the ability to anticipate the introductions of emerging technologies and procedures.

In this context, on March 21, 2022, *Law n. 14,313*<sup>5</sup> was enacted, introducing changes in the processes of technology incorporation and in the utilization of drugs, within the SUS, with recommendation that differ from the market approved indication sanctioned by the Brazilian Health Regulatory Agency (Anvisa)<sup>5</sup>.

The changes affected the two items of Article 19-T of *Law n. 8,080*, already modified by *Law n. 12,401/2011*<sup>2</sup>, which regulated the availability of medicines, national or imported, without market approval by Anvisa or for use other than the package leaflet indication. In the new *Law n. 14,313/2022*, dispensation, payment, and reimbursement of products with indication other than the market approved one are authorized, provided that CONITEC recommends their use and that they follow standards in Brazilian Ministry of Health protocols.

The enactment of *Law n. 14,313/2022* is an evolutionary scenario of regulatory changes in Brazil, beginning with *Decree n. 8,077/2013*<sup>6</sup>, which made registration more flexible. Up until then, CONITEC consulted Anvisa on the safety and efficacy of drugs or market approved products in cases where the indication of intended use was different from approved indication of use. This step was mandatory when defining what should or should not be incorporated into the SUS<sup>6</sup>.

The new rule also includes *Decree n. 11,161*, of August 5, 2022<sup>7</sup>, which, regulates the new Law and introduces several amendments in *Decree n. 7,646/2011*<sup>8</sup>. Thus, the operational structure of CONITEC was reformed, extinguishing the Plenary and fragmenting the evaluation and recommendations into three different Committees (one of which is of Medicines), in addition to increasing the number of individuals involved in the process, incorporating representatives of the Brazilian Medical Association (ABM) and the HTA Centers, part of the Brazilian Network for Health Technology Assessment (REBRATS)<sup>7</sup>.

Regarding the incorporation of drugs not market approved by Anvisa, the new Decree links this type of request to the competent areas of the Brazilian ministry of Health, requiring proof of efficacy, effectiveness, and safety of the intended indication. However, it introduces the concept of “consecrated use” – an undefined term that jeopardizes the paradigm of evidence – and admits authorization of intended use by an external regulatory agency, provided that the agency is a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) or the International Medical Device Regulators Forum (IMDRF)<sup>7</sup>.

The market approval grant must be linked to proof of quality, safety, and efficacy, but the specific recommendation of use may not be the only one possible. Other indications may later be submitted, expanding the use for age group or stage of illness other than what the medicines was initially approved for, or even expanding its use to other clinical conditions. However, all cases required evaluation (and approval) by Anvisa<sup>9</sup>.

The change has generated concern and different manifestations<sup>10</sup>. Among these, we highlight a March 22 release from Anvisa, which signals that “*the application of the new law requires robust actions of the government to reduce risks to patients*”. Expanding use outside the conditions approved in the package leaflet – without support from the agency’s technical-scientific analysis – may result in unknown risks. Although it expresses respect for the established constitutional legislative process, the release also informs that the agency was already studying the “*adoption of regulatory measures for monitoring purposes, aiming at the protection of public health*”<sup>11</sup>.

The request for medicines for unapproved uses constitutes an important part of the lawsuits for access to medicines, in 2013, it was already expected that the incorporation process would increase judicialization<sup>12</sup>. Prescribers are constantly influenced by the pharmaceutical industry in order to adopt off-label uses, a constant result of the incorporation of new drugs. Part of this use can be justified by the severity of the case, absence of adequate dosage forms for the patient, lack of response to conventional therapy, or lack of therapeutic options<sup>13</sup>.

Faced with the notion that the new rule may favor pressures to incorporate new technologies, including those not market approved, their impacts on judicialization become potentially significant. CONITEC’s expanded indication rulings are sometimes morose, even if evidence of efficacy

supports use. However, this is not always accompanied by evidence of safety, linking off label use to health risks<sup>9</sup>.

According to Art. 38 of Anvisa's *Resolution RDC n. 200/2017*<sup>14</sup>, it is necessary to submit a Brazilian Pharmacovigilance Plan by the the market holder to Anvisa, whenever a new indication of use for a drug is requested. A Brazilian Risk Mitigation Plan may also be requested by the agency if there are questions about the safety of the proposed new indication and if a drug is already available abroad, for which an updated Pharmacovigilance Report should also be submitted.

The evaluation of the Brazilian Pharmacovigilance Plan, Brazilian Risk Mitigation Plan and the updated Pharmacovigilance Report, prior to the authorization of a new indication by Anvisa, aims to ensure that the precepts of good pharmacovigilance practices will be applied by the market holder for the new use, including definition of safety specification, provision for the collection and processing of all information on notified adverse events, and submission of periodic reports of the benefit-risk ratio of the medicinal product, in accordance with *RDC n. 406/2020*<sup>15</sup>.

This obligation is not foreseen for market holders in off label – i.e., unregistered – use, which reduces periodic monitoring actions of product performance. Collection and processing of data on the adverse event of a new use by the market holders of an already approved medicine are fundamental for risk management and continuous monitoring of the benefit-risk profile, particularly important in cases of use in the targeted populations (children, older adults, pregnant women, specific patients), or in a dosage or therapeutic range other than that already approved by Anvisa. Mandatory market recall of medicine would be recommended when the risks outweigh the benefits.

Other aspects make up the context of the new legislation. One is the panorama of drug shortages in Brazil, which includes a constant lack and even discontinuity of several essential items, from primary care medicines to those used in high-complex care. There is pressure to modernize the therapeutic framework, a kind of “therapeutic transition”, removing from practice old drugs that are still effective, but with relatively low price, and replacing them with more advanced alternatives, much more expensive and of greater interest to the industry. Another is the proposal to transfer the price regulation from the Drug Market Regulation Chamber (CMED) and Anvisa, to the Brazilian Ministry of Economy<sup>16</sup>, which could lead to sanitary “deregulation”. Both movements favor the market.

Worldwide, the decision on the risk-benefit profile of a drug and the approval of its different uses are exclusive prerogatives of regulatory agencies. The aspects indicated by the new legislation, which facilitate expanded indication, “institutionalizing” the off-label use, and fragment the evaluation processes of health technologies, generate concern. The process of evaluating medicines may now dispense with Anvisa's regulatory action, which would be even more significant in the present context, given that the various issues regarding the responsible application of the new legislation were not properly discussed in the field of public health.

## Contributors

R. Caetano contributed to the study conception, analysis of standards and context, writing, and critical review of the content; approved the final version; and is co-responsible for the content and integrity of the manuscript. L. C. Lopes contributed to the study conception, analysis of standards and context, writing, and critical review of the content; approved the final version; and is co-responsible for the content and integrity of the manuscript. G. M. L. Santos contributed to the study conception, analysis of standards and context, writing, and critical review of the content; approved the final version; and is co-responsible for the content and integrity of the manuscript. C. G. S. Osorio-de-Castro contributed to the study conception, analysis of standards and context, writing, and critical review of the content; approved the final version; and is co-responsible for the content and integrity of the manuscript.

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## Conflict of interest

One of the authors is career civil servant of Brazilian Health Regulatory Agency.

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