Practical application of regulatory science by Latin American regulatory agencies: optimising the use of advisory committees in the Colombian regulatory environment

This Briefing provides an overview of how advisory committees can be used to support the regulatory decision-making process and considering the context of Latin American regulatory systems, aims to better understand the operation of Colombia´s Reviewing Commission (Comisión Revisora), an advisory body created to advise the Ministry of Health together with the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA).

Based on our analysis, several recommendations can be considered to optimise the effectiveness of the Comisión Revisora and to help address unmet medical needs:

- Focusing the activities of the Comisión Revisora to selected types of innovative products
- Using external expert advisors for specific therapeutic areas
- Having the Comisión Revisora serve in a truly advisory capacity and not as an assessment body
- Optimising the flow of information between the Comisión Revisora and INVIMA to help reduce delays.

Considering INVIMA´s relevance as a PAHO regional reference agency, its active participation in ICH and the importance of improved access to innovative therapeutic treatment options, additional recommendations have emerged:

- Optimise the regulatory landscape by facilitating the submission and efficient assessment of dossiers for unmet medical needs.
- Promote, develop, and maintain evaluation guidelines and requirements that are aligned with international standards.
- Increase communication and discussions with sponsors, as recommended by WHO and ICH international practices.
- Strengthen processes that accelerate access to innovative medicines for unmet medical need, particularly using reliance mechanisms.
- Reinforce INVIMA´s path towards international convergence and harmonisation with best international practices.

Este informe presenta un panorama general sobre como los comités asesores pueden mejorar el proceso de toma de decisiones regulatorias. Al tomar en cuenta el contexto de América Latina, profundiza en la situación operativa de la Comisión Revisora en Colombia, la cual fue concebida como un órgano asesor del Ministerio de Salud y del Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) de Colombia.

Algunas recomendaciones de este informe que podrían optimizar la efectividad de la Comisión Revisora y apoyar en atender necesidades médicas no satisfechas son:

- Enfocar las actividades de la Comisión Revisora hacia ciertos productos innovadores seleccionados
- Enfocar el apoyo de expertos externos hacia áreas terapéuticas innovadoras
- Encausar a que la Comisión Revisora actúe en su papel de asesor más que como una organización dictaminadora
- Optimizar el flujo de información entre la Comisión Revisora el INVIMA para reducir los retrasos regulatorios.

Considerando la relevancia de INVIMA como agencia de referencia regional de la OPS, su activa participación en la ICH y la importancia de mejorar el acceso a opciones terapéuticas innovadoras, surgen las siguientes recomendaciones adicionales:

- Optimizar la estructura regulatoria para facilitar la entrada de nuevas solicitudes y lograr una evaluación eficiente de las solicitudes referentes a necesidades médicas no cubiertas.
- Promover, desarrollar y mantener la existencia de guías regulatorias y requisitos claros y alineados con estándares internacionales.
- Mejorar la comunicación y el diálogo con los solicitantes, tal como lo recomienda la OMS y las prácticas internacionales de ICH.
- Fortalecer el acceso a medicamentos innovadores para necesidades médicas no cubiertas, especialmente utilizando mecanismos de “reliance”.
- Fortalecer el avance de INVIMA hacia la convergencia y armonización regulatoria con mejores prácticas internacionales.

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CIRS Centre for Innovation in Regulatory Science

Introduction

Regulatory agencies are entrusted with making sound, science-based decisions about the quality, safety and efficacy of medicines to be used by their society. The decision-making process is complicated, multifactorial and encompasses the evaluation of often complex products, requiring the assessment of diverse types of data spanning animal pharmacology, human clinical studies, pharmacokinetics, manufacturing and quality, and labelling considerations. Even the most well-resourced and mature agencies can be faced with situations in which having independent input into the decision-making process from specialist advisors can add an additional level of expertise, vision and confidence to the agency's regulatory decision. This supplementary input is typically provided through an advisory committee process.

Trust in how regulators and their advisory committees address issues that arise during market authorisation assessment is a foundational element of the integrity of the regulatory system (1). To benefit from additional expertise, most agencies can either formally or informally, seek the advice of external advisors. Contributions to the decision-making process can occur on an ad hoc basis, with academic and clinical experts being asked to advise on a specific issue. In addition, having well-functioning external advisory committees is an important part of quality decision making in medicine regulation, particularly for small- and medium-sized regulatory authorities, who may not have specialised technical expertise available internally. For example, advice in study design, biostatistics and population pharmacokinetics may be required. This advice is increasingly important as new therapies become more specialised, such as in oncology and rare disease treatment. Furthermore, the "real world" experience of physicians in general practice and of patient representatives on committees is just as valuable as the advice of technical specialists (1).

Many agencies have formalised the advisory process through the development of speciality Working Parties, such as the European Medicines Agency's (EMA) Scientific Advice Working Party (SWAP), or standing advisory committees dedicated to a specific function or therapeutic area, as are designed to support the US Food and Drug Administration (FDA). The Australian Therapeutic Good Administration (TGA) improves its decision-making practices by using external advisory committees that provide critical input into the quality of the final decision by advising on a range of clinical and patient factors (1).

Not all committees provide only advice; some perform assessments on behalf of or together with the agency. For example, the Turkish regulatory agency uses an extensive network of thirty advisory committees responsible for the scientific assessments of the products including medicines, medical devices, and cosmetics. The committees consist of internal experts from the agency's staff and external experts from universities. The required skills for committee members are detailed in the legislation "Regulation on the Establishment and Roles of the Turkish Medicines and Medical Devices Agency's Scientific Advisory Committees.". The committees meet weekly with the agenda to scientifically review submitted data prepared by the agency's staff, but there is no target time for their scientific assessments. For a product that has already been approved/registered by another authority, the review process starts with the assessment by the Clinical Evaluation Committee. Following the committee's positive decision, the submission is then reviewed by the Bioavailability and Bioequivalence Committee, Pharmacological Evaluation Committee, and Quality Evaluation Committee, in parallel. Questions related to the application can be raised by the experts throughout the review process and are sent to the applicant separately, not as a batch (2).

The benefits of relying on the input of advisory committees, especially for treatments addressing an unmet medical need, have been well documented. For example, in one study, the FDA averaged about 5 months faster in the review of novel monoclonal antibodies when compared to the EMA. This difference may have been due to the multi-step process that the EMA must follow, compared to the more flexible pathways available to the FDA. Even when requiring input from external advisory committees, the FDA system may be more efficient than EMA's; this improved efficiency should benefit patients as well as sponsors (3). Indeed, positive advisory committee recommendations (outcomes) were found to be a predictor of a positive regulatory authorisation outcome for products that addressed rare or serious illness (4).

While advisory committee voting patterns are usually predictive of the final decision made by the regulator, committees do have several potential drawbacks. Members are typically only part-time appointees and may be less informed on the detailed regulatory context than an evaluator who may have spent months considering a submission.

In addition, clinical or academic members of committees may not always consider issues from a regulatory or population health standpoint (that is, through a systematic analysis of benefits/harms/uncertainty). There are other factors that could apply to any type of committee. For example, an authoritative member with professional standing in the field could hold sway or alternatively, a poorly informed but strongly opinionated member can unduly influence others. Newer committee members may feel reluctant in presenting a differing view about a product if they follow an internationally recognised expert in the meeting agenda. Even within committees that formally vote on product submissions, such as some of US FDA, influences of this type may persist, as secret ballots are usually not used on these regulatory advisory committees. It is also unclear whether an impact on debate and decision making is created by holding advisory committee meetings in public versus in private (1).

With this background, we sought to better understand how advisory committees are used in the context of some Latin American regulatory systems. Table 1 highlights key characteristics of committees in selected Latin American countries and Canada (for comparison). We observed several interesting findings in this cohort. For example, some committees (Chile, Canada) are advisory in nature providing their insights to the agency, with the agency taking their input into account in its final decision-making process. In other countries (Colombia, Mexico), the committee performs the function of a reviewer, assessing the content of the marketing authorisation application, and providing a committee-based decision on the quality, benefits and risk of the products and its ultimate authorisation recommendation.

	Colombia	**Chile**	**Mexico**	**Canada**
Name of Advisory Board	Reviewing Commission	Expert Committee	New Molecules Committee	Ad-hoc
Origin of experts	Internal and external	Internal and external	Internal and External	External
Implications of assessment	Decision**	Advise	Decision	Advise
Scope	NCE, biologics, new: indications, associations, concentrations, pharmaceutical forms, protocols, bioavailability and bioequivalence studies, etc.	New products, new: indications, new routes of administration	New small molecules, new combinations, new therapeutic indications, and all biologics	Ad-hoc
Experts' main place of work	Universities	Universities and clinical centres	Universities	Universities and research centres
Compensated	Yes	No	No	No

Table 1. Comparison of key characteristics of advisory committees in selected regional agencies (7)

** The Comission was created as an advisory body, however, considering its exclusive mandate over safety and efficacy assessment, its opinions become regulatory decisions.

Understanding the Reviewing Commission in Colombia

In Colombia, scientific advice is provided through the Reviewing Commission (Comisión Revisora), an advisory body created to advise the Ministry of Health together with the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA). In particular, the Comisión Revisora is responsible for issuing recommendations and implementing criteria for scientific and technical matters in health-related issues.

The Comisión Revisora was created by the Ministry of Health of Colombia. The Executive Board is responsible for establishing and modifying the functions and composition of the Comisión and is in charge of selecting its members. The Executive Board is chaired by the Health Minister or its assigned delegate (6) and also includes:

- The Minister of Trade Industry and Tourism
- The Minister of Agriculture and Rural Development
- The Director of Medicines and Health Technologies of the Ministry of Health
- The Director of the National Health Institute (INS)
- A local Minister of Health designated by the Ministry of Health
- A representative of the scientific community designated by the Ministry of Health.

The Comisión Revisora was originally created in 1975 (Decreto Ley Nº 981) as an Advisory Council for Technical Issues for the Ministry of Health. The Comisión Revisora evolved throughout the years with adjustments and changes through different decrees, resolutions and other regulations. The latest Accord establishing the organisation and functions of the Comisión Revisora was Acuerdo 003 of 2017 of INVIMA. This important Accord was consistent with Pan American Health Organisation (PAHO) recommendations to improve INVIMA´s processes, separate the functions and define the committees that support the Comisión Revisora, as well as list the functions and requirements of the members of each committee.

The Comisión Revisora is composed of the following specialised committees:

1. Specialised Committee on new molecules, new indications and biologic products (SCNMB)
2. Specialised Committee on Medicaments (SNM)
3. Specialised Committee on herbal medicines and dietary supplements
4. Specialised Committee on homeopathic medicines
5. Specialised Committee on food and alcoholic beverages
6. Specialised Committee on medical devices and in-vitro diagnostics

This Briefing focuses on the Specialised Committee on new molecules, new indications and biologic products (SCNMB) and the Specialised Committee on Medicaments (SNM) because of the implications for the access of innovative medicines and other medicines. The members of the SCNMB also participate in the SNM. Their functions include:

- Pharmacologic evaluation of safety and efficacy of New Chemical Entities and biologics
- Pharmacologic evaluation of safety and efficacy of biologics
- Pharmacologic evaluation of safety and efficacy of new indications, new associations, new concentrations and new pharmaceutical forms
- Approval of protocols, bioavailability and bioequivalence studies and modifications implying pharmacokinetic changes
- Approval of changes to sales conditions and to the administration route
- Technical analysis to assess new medicines to be added to the national List of Essential Medicines

As indicated in Art. 27 of Decree 677 of 1995, the pharmacologic evaluation of therapeutics is an exclusive function (the Spanish term indicated is “privativa”) of the Specialised Committee.

Considering the above features of the Comisión Revisora, it is useful to highlight some of its important characteristics:

- The Comisión Revisora functions as a parallel body to INVIMA, with differentiated and complementary responsibilities with respect to the assessment of submissions.
- The Comisión Revisora is closely linked to INVIMA but organisationally is a separate body and the accountability of its performance is with the Executive Board chaired by the Ministry of Health. Contrary to this situation, most (if not all) agencies have internal responsibility for the final evaluation of submissions.
- The Comisión Revisora has specific responsibility for the assessment of the safety and efficacy parts of the submissions. Consequently, the Comisión Revisora operates more as a decision-making rather than an "advisory" body.
- Like INVIMA, the Mexican agency has an advisory body (New Molecules Committee, NMC) whose assessments serve as a decision for the agency. The NMC, however, has a more limited scope of activity than the Comisión Revisora.

Optimising the availability of products for unmet medical needs

There is no single, widely adopted definition of "unmet medical need". Therefore, the criteria that will be applied to assess a product in one jurisdiction may differ from those of another. The criteria that can help define unmet medical need are varied and can include: stakeholder perception of the need; stakeholder expectations of the types of therapies to be made available; the nature of the disease and its course over time; the current local standard of care; the available alternative therapies; and the 'patient disease journey', among others. While patients with rare, orphan or other unmet needs today have the expectation that a therapy available in one or more jurisdictions should be similarly available in their country, the reality is that this availability varies widely across countries and regions.

We decided to study to what extent unmet medical needs products approved in EMA and FDA between 2017 and 2018 reached Latin American countries as of September 2020. For this purpose, we defined unmet medical needs products as those approved by both FDA and EMA that comply with the following conditions: (1) the product was processed in either agency through an expedited pathway, (2) the product was classified as orphan drug. Consequently, we identified 23 therapeutic products which could be classified as unmet medical products approved by both FDA and EMA during 2017 and 2018. Of that cohort, about 40% were cancer treatments, 17% for blood related illnesses and 13% were antibiotics. It is interesting to note that almost 40% (n= 9) of the 23 products were approved in Brazil and 13% (n= 3) were authorised in Chile. In contrast, Colombia and Mexico did not register a single approval from the same cohort of products (though we do not know if those products were in fact submitted to each country). Whether the activities of the respective advisory committees have had an impact on the regulatory decision could be a factor that requires further exploration. Considering that none of these products have yet been registered in Colombia and Mexico, the delays that have been associated with the activities of the Comisión Revisora of Colombia and the lack of meetings taking place for the New Molecules Committees in Mexico may be playing a role.

Many factors can influence the timeline in which a product that addresses an unmet medical need is authorised for use by a country. Figure 1 illustrates this heterogeneity. Across a cohort of new molecular entities (including those for unmet medical need) assessed by CIRS for the period of 2014-2018 (unpublished data), we observed that the median time from the date of first approval (anywhere in the world) to submission to the assessed countries ("Lag Time"; in red) ranged from 37 days (Brazil; indicating the median submission occurred about a month after the first-in-world authorization) to 246 days (Mexico). Factors that may have influenced this Lag Time include the submission capabilities and strategies of the respective multinational companies, the nature of the product (e.g. are special storage conditions required), the nature of the target medical market, and perhaps most important, the regulatory environment in that country. For example, the Certificate of Pharmaceutical Product is not required at the time of the dossier submission in Brazil, facilitating the submission process (shown as a low Lag Time). Nevertheless, the authorisation process (both agency and company time, in yellow) was quite long in Brazil. Colombia is characterised by a long Lag Time comparable to that of Argentina and Mexico but coupled with the longest assessment time among these countries.

In Mexico, the use of the NMC had in the past provided an effective route to assess a new molecule and to allow the agency (COFEPRIS) to make the final authorisation. We found a median approval time of 224 days for new molecule authorisations across all authorisation pathways. However, with the disbandment of the NMC in 2019 and its slow re-organisation, assessment times have increased in 2020 with much of the delay being due to the non-activity of the NMC. Long assessment times can often be associated with workload backlogs; these have become especially acute during 2020 because of staff limitations due to COVID-19 infections and the diversion of manpower to products and therapies that require emergency attention to combat the pandemic. Other causes of regulatory delays include inherent structural inefficiencies, not using reliance pathways to permit the agency to focus on added-value activities, and bottlenecks resulting from the use of advisory committees. In Colombia, factors such as the organisational structure of the agency (INVIMA), the unique assessment process that addresses technical (safety and efficacy), chemical/product, and health technology assessment considerations, and the role of the Comisión Revisora in the authorisation process, could be investigated in more detail to determine if greater efficiencies could be built into these processes, thereby optimising patient access to quality, safe and effective medicines, especially when alternatives are few or lacking.

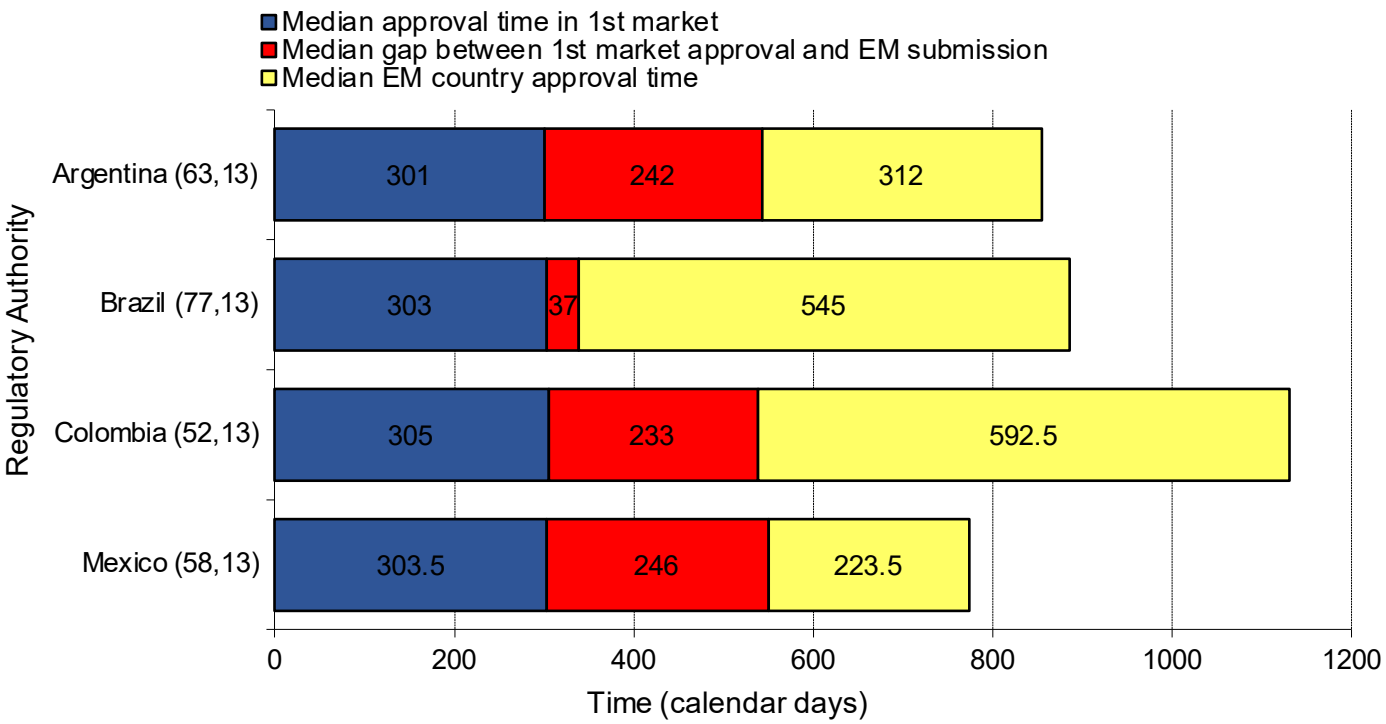

Figure 1. Median time to roll out to selected Latin American countries for New Active Substances approved between 2014 and 2018.

n in bar = median number of days; (n1,n2) = number of NASs, number of companies

NASs included in this analysis include those with first world submission, first world approval, application submission and application approval dates only.

Recommendations for optimizing access to innovative therapies for unmet medical needs

This analysis has provided an overview of how advisory committees can be used to support the regulatory decision-making process. Quality decisions can be made when a structured process is consistently followed in an effective and efficient manner. Advisory committees can provide the specialised expertise to support the regulatory process. However, these committees can also be a bottleneck.

With the wealth of experience by agencies around the world on using advisory committees, some “Best Practices” can be considered. In recognition of the many committees that interact with US agencies, US Congress, created an Act governing how government advisory committees should be organised and managed (5). This helped to bring consistency to their processes and could serve as a model for other advisory committees around the world. Fortunately, the Act is written sufficiently broadly to give each agency flexibility in how it can establish administrative guidelines and management controls for their advisory committees yet recognising that these must be consistent with directives of the Act. For example, the agency needs to systematically gather information on the nature, functions, and operations of their advisory committee(s); their meetings must be open to the public; detailed minutes of each meeting of the advisory committee meeting must be kept (and include a record of the persons present, a description of matters discussed, and conclusions reached). Furthermore, copies of all reports received, issued, or approved by the advisory committee are to be made publicly available. The Global Benchmarking Tool (GBT) for regulatory agencies of the World Health Organisation considers various indicators related to the use of committees. For example, GBT sub-indicator MA04.05 examines if 'An advisory or scientific committee, including external experts is involved in the review of marketing authorisation applications".

Several recommendations can be considered to optimise the effectiveness of the Comisión Revisora and to help address unmet medical needs:

- Focusing the activities of the Comisión Revisora to selected types of innovative products
- Using external expert advisors for specific therapeutic areas
- Having the Comisión Revisora serve in a truly advisory capacity and not as an assessment body
- Optimising the flow of information between the Comisión Revisora and INVIMA to help reduce delays in the regulatory process

Considering INVIMA´s recognition as a PAHO regional reference agency, its active participation in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the value of innovative therapeutic treatment options in bringing significant health benefits to society and patients, it is additionally recommended to:

- Optimise the Colombian regulatory landscape by facilitating the submission and efficient assessment of dossiers for products for unmet medical needs.
- Promote, develop, and maintain evaluation guidelines and requirements that are aligned with international standards.
- Increase communication and discussions with sponsors on their applications, as recommended by WHO and ICH international practices.
- Strengthen processes that accelerate access to innovative medicines for unmet medical need, particularly using reliance mechanisms.
- Reinforce INVIMA´s path towards international convergence and harmonisation with best international practices.

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The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

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