FIFARMA
Federación Latinoamericana de la Industria Farmacéutica

Regulatory Issues in the context of Health Emergencies – Potential Approaches to address Challenges for the Latin American and Caribbean Region

An industry perspective – feedback from FIFARMA member companies

Products in scope: Vaccines and Medicines – COVID-19 and non-COVID-19 Therapies

The R&D-based biopharmaceutical industry in Latin America and the Caribbean seeks to work in partnership with PAHO and National Regulatory Authorities (NRAs) to ensure the ongoing supply of medicines and vaccines to the best of our ability to patients at a time when 'normal' production, supply chains and business operations are adversely impacted and massively challenged. We recognize that the ongoing COVID-19 pandemic poses challenges to all NRAs in the region both in the short and medium term.

FIFARMA would therefore like to share our commitment to the following regulatory priorities across the region:

- *Working in partnership and collaboration with NRAs to define the best science-based regulatory strategies for ensuring the availability of COVID-19 medicines and vaccines*
- *Maintaining supply of non-COVID-19 medicines and vaccines*
- *Ensuring all our medicines and vaccines continue to meet appropriate standards for quality and safety*
- *Progressing research into new treatments and prevention of COVID-19 and of other conditions*

As a key stakeholder in the healthcare system, we recognize that there are differing capacities across NRAs in the region and we have identified several potential challenges and issues that could impact regulatory processes in the region. In this paper we outline these issues and propose some potential approaches for NRAs to consider when implementing strategies to address these in the short and medium term.

We welcome the efforts by PAHO and several NRAs in the region who have already taken forward a number of these measures in their efforts to ensure patients continue to access safe, effective and high-quality medicines during the current health emergency. We would support ongoing transparency of these actions for all stakeholders to maximize implementation and further aid alignment in managing these regulatory issues across the whole region. We also note

that while some of these actions identified below are strictly for the short and medium term, some may provide an opportunity for NRAs to strengthen their regulatory systems through implementing elements of Good Regulatory Practices in the longer term.

General Considerations

Reduced personnel and work capacity: In the context of public health emergencies, reduced personnel will result in reduced work capacity. Furthermore, the partial or complete closure of government and private institutions in most countries, in addition to limitations such as travel restrictions, can impact the normal functioning of NRAs. This may completely impede some regulatory processes if these cannot be carried out remotely and ultimately impact medicines supply in the longer term.

Use of digital tools for communication: Many NRAs require physical visits for some regulatory processes. Optimizing the use of digital tools for communication - as simple as enhancing the use of emails for receiving documentation, sending notices to applicant electronically, or allowing for the possibility of having remote meetings with regulators - could have a major impact. Not having procedures in place for using online platforms for some regulatory activities (from approval to life-cycle management) will have an impact on implementation of changes and licenses renewals leading to problems with product import/export. More specific to the context of a public health emergency, using electronic forms to collect information (such as on potential shortages) can speed up the process of information gathering. Platforms for virtual meetings should be used as a means for the continuation of routine regulatory exchanges between industry and NRAs.

Acceptance of electronic documents: Promoting and facilitating the acceptance of electronic documents (e.g. eCPP, eGMP) instead of requiring a wet ink signed original/ physical copy is also something that would greatly impact these processes. Waiving wet signatures (e.g. acceptance of e-signatures) and legalization requirements would support the continuity of regulatory processes. NRAs should also consider, where possible, also waiving the need to provide these documents as a future post-pandemic commitment.

Communication with Stakeholders: NRA decisions become more critical and visible during epidemics. Regular, high level meetings between NRA and Industry associations allow rapid discussions on any new emerging risk for the operation of the Regulatory System. Ideally any change to NRAs operations, regulations, special agreements or criteria should be published

and properly communicated to the population, industry, authorities, and other relevant stakeholders. Clear, public and transparent communications will promote and ensure regulatory compliance in related activities such as public tenders, IP protection, international trade, official inspections.

Table 1: Summary of General Considerations – Challenges and potential approaches to consider

CHALLENGE	POTENTIAL APPROACHES TO CONSIDER WHEN ADDRESSING THESE CHALLENGES	RECOMMENDATIONS FOR IMPLEMENTATION
Limited working capacity within the National Regulatory Authorities that may create 'backlogs' in processes that ultimately impact medicines supply.	Digital technology solutions to enable remote working with the appropriate requirements for safety and confidentiality	SHORT & MEDIUM-TERM
	Increase and strengthen capability of NRA employees on available digital tools and best practices for ways of working when working from home/ virtually	
	Implementation of reliance and work sharing mechanisms	SHORT & MEDIUM-TERM
	Prioritization when issuing or updating future regulations and guidance	SHORT & MEDIUM-TERM
Requirements for face to face exchanges with NRAs	Optimizing the use of tools as such as email or platforms for virtual meetings	SHORT & MEDIUM-TERM
Requirements for printed documents & legal certification	Waiving wet signatures and legalization requirements where legislation allows • Accept digital signatures instead of wet signatures • Consider waiving the requirement to provide these original and legalized	SHORT-TERM

	documents as a commitment post pandemic	
	Acceptance of submissions using digital copies in place of paper-based submissions with the appropriate requirements for safety and confidentiality	SHORT & MEDIUM-TERM
Lack of communication with impacted stakeholders	High level meetings between NRA and Industry associations to highlight any new emerging risk for the operation of the Regulatory System	SHORT & MEDIUM-TERM
	Clear, public and transparent communication by NRAs e.g. publication of any changes to its operation, regulations, special agreements or criteria	SHORT & MEDIUM-TERM

Regulatory Processes (Product Registrations, Renewals, Lifecycle Management, Inspections, Post-Market Surveillance)

Need for fast-track processes for COVID-19 therapies: NRAs should consider the adoption of fast track regulatory processes related to COVID-19, as well as other measures such as promotion of programs for compassionate use and named patient supply. NRAs may wish to allocate special group(s) of evaluators for review of submissions related to COVID-19 and to facilitate discussions with industry. Waivers for country specific requirements not routinely part of the Common Technical Dossier (CTD) submitted to Trusted/Reference Regulatory Authorities may facilitate earlier submissions within the region.

Managing impact on routine regulatory processes: The current pandemic scenario and the constraints in the operation of NRAs call for adaptive approaches to regulatory submissions and post-market activities. Regulators should ensure the continuity of submissions for approvals, renewals and post-approval changes (PACs), including quality and labelling changes, as well as the reporting of adverse events, Periodic Safety Update Reports (PSUR) and other safety reports. Industry has observed that during health emergencies some countries stop many routine regulatory processes which may have unintended consequences in the longer term[1].

- A key opportunity to tackle this issue is implementing reliance mechanisms across the product lifecycle, which should go going beyond their use solely for Emergency Use Authorization of Medicines and Other Health Technologies during a Pandemic. Reliance and work sharing mechanisms provide a tool for NRAs to better manage resource capacity issues whilst simultaneously strengthening regulatory systems. NRAs are encouraged to make use of the PANDRH document "*Regulatory reliance principles: concept note and recommendations*", and to make use of these mechanisms for approvals and post-approval changes (PACs).

- For "non-critical" regulatory procedures, such as maintaining existing marketing authorizations or license to operate, automatic renewals or extended grace periods can be considered until the NRA can review applications again. For PACs, NRAs can introduce flexibilities in the grace period implementation after PACs are approved - being able to supply with the current version until stocks are depleted. NRAs should consider handling PACs with no impact on quality, efficacy and safety via notifications, with no need for prior approval.

- In some cases, regulatory authorities only proceed with a regulatory review process upon receipt of a sample or after registration testing. During a pandemic, with the disruption of supply chains, temporarily waiving of the need for samples and registration testing would help speed up the review process and ultimately access of medicines to patients.

- Due to constrains like travel restriction, conducting on-site inspections may need to be paused and a risk-based approach taken to identify 'mission critical inspections' and selection of the most appropriate risk-based alternative solution. Reliance in GMP certificates issued by other NRAs should be considered, as well as the possibility to perform virtual/paper-based inspections" also known as "remote desktop review[2]". For the latter, it is paramount that NRA gives full transparency to sponsors of the items to be observed during the inspection.

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Table 2: Summary of Regulatory Processes (Product Registrations, Renewals, Lifecycle Management, Inspections, Post-Market Surveillance) – Challenges and potential approaches to consider

CHALLENGE	POTENTIAL APPROACHES TO CONSIDER WHEN ADDRESSING THESE CHALLENGES	RECOMMENDATIONS FOR IMPLEMENTATION

Fast track regulatory processes related to COVID-19	Accelerate Market Authorization Approvals (MAA) for new COVID-19 treatments (including antivirals & Intensive Care Unit (ICU) products) MAs:
	• Label these fast track regulatory processes as "COVID-19 URGENT"
	• Make use of Emergency Use Provisions and Reliance mechanisms[3] where appropriate
	  ○ Allow fast acceptance of products with valid MAs from trusted/reference countries using all available regulatory tools
	  ○ Waivers for country specific requirements not routinely part of the Common Technical Dossier (CTD) submitted to Trusted/Reference Regulatory Authorities
	• Compassionate use, named patient supply programs
		SHORT-TERM

	For post-approval changes: • Label these fast track regulatory processes as "COVID-19 URGENT" & utilize reliance mechanisms where appropriate • Follow a risk-based approach for some post-approval changes	SHORT-TERM
Ensure continuity of regulatory processes while	Temporarily adapting approach to post-market surveillance e.g. reporting of adverse events, PSUR and other safety reports in a risk-based fashion	SHORT & MEDIUM-TERM
	Temporary adopt alternative approaches for regulatory submissions such as new MAA, renewal	SHORT & MEDIUM-TERM

undertaking pandemic response	processes and post approval changes including quality and labelling changes e.g. • PACs with no impact on quality, efficacy and safety could be handled via a notification • Possibility to suspend ongoing processes and allow more time to provide answers to questions.	
	Temporary implementation of automatic renewals for marketing authorizations and licenses to operate	SHORT TERM
	Temporary extension of "grace periods" for the implementation PACs including quality and labelling changes	SHORT-TERM
	Temporary waving of sample requirements and registration testing	SHORT & MEDIUM-TERM
	Implementation of reliance and work sharing mechanisms (for approvals and PACs)	SHORT & MEDIUM-TERM
Inability to carry out GxP-related activities in person	Acceptance of a temporary risk-based approach to GMP activities by regulatory authorities and market authorization holders e.g. • Retain the right to operate by extending and clarifying the validity of GMP certificates that are perceived as close to, or past, a "3-year expiry date", Or • Acceptance of alternative documentation when a GMP certificate is not available or expired.	SHORT & MEDIUM-TERM
	Adopt reliance mechanisms (e.g. PIC/S)	SHORT & MEDIUM-TERM
	Performance of 'virtual/paper-based inspections' also known as "remote desktop review"	SHORT & MEDIUM-TERM

Maintaining Supply

Demands for many medicines change in the context of public health emergencies, possibly causing disruptions in the supply chain of essential medicines. There are practical key considerations that NRAs should have in mind to enable streamlined processes for upscaling production, timely customs and release procedures, and labelling requirements.

Upscaling production: There are regulatory measures that pose barriers to quickly upscaling production, and a health emergency e.g. pandemic scenario might require flexibilities around activating new or additional production sites or suppliers or increasing batch sizes. These could be achieved through reliance mechanisms or accelerated implementation of new regulations

that can facilitate upscaling production. Allowing multiple sites to be included in the same marketing authorization can minimize supply disruption[4].

National Stockpiling: Some countries opt for stockpiling and procuring large amounts of products or putting a ban on exports in emergency contexts. Avoiding unnecessary national stockpiling of medicines, vaccines, diagnostics and medical devices helps support supply continuity. Another potential solution is giving the manufacturer flexibility on minimal stockpiling requirement. Duplicative queries on supply chain status should ideally be limited by taking a regional approach, where possible, generating consolidated requests, with one point of contact.

Customs/Import/Release: Fast tracking on customs procedures and local release operations is essential to ensure a reliable supply of medicines. This can be achieved by ensuring "green" lanes for medical supplies even under complete border closure; decreasing high-shelf life requirements at the time of import; temporary risk-based waiving of in country import testing or accepting receipt on Certificates of Analysis (CoA) / testing by other parties.

Labelling: Regulatory flexibilities around labelling can be helpful in different scenarios, for instance when products intended to be deployed in one country are now needed to be sent to another one. Acceptance of multi-country packaging e.g. allowing for text deviations, the possibility of using stickers[5], or facilitating the implementation of e-labelling (i.e. allowing digital formats of the Patient Information Leaflets (PILs) in the local language, when available) can provide a solution. NRAs may wish to develop a national portal for approved prescription drug information. Non-country specific labelling/neutral labelling and flexibility on required stamps/barcodes/pack sizes can also make a difference. Industry is committed to working closely with NRAs to ensure that labelling flexibilities are adequately addressed to avoid traceability issues and any increased risk of falsification.

Table 3: Summary of Maintaining Supply – Challenges and potential approaches to consider

CHALLENGE	POTENTIAL APPROACHES TO CONSIDER WHEN ADDRESSING THIS CHALLENGE	RECOMMENDED TIMELINE
Regulatory barriers to	Flexibility around activating new, alternate or additional production sites or suppliers.	SHORT & MEDIUM-TERM

upscaling production	Flexibility around increasing batch sizes.	
Measures that prevent fast deployment of products in the market	Avoiding unnecessary national stockpiling of medicines and allowing manufacturers flexibility on minimal stockpiling requirements	SHORT & MEDIUM-TERM
	Fast tracking on customs procedures and local release operations	SHORT TERM
	Ensuring "green lanes" for medical supplies	SHORT & MEDIUM-TERM
	Temporarily decreasing high-shelf life requirements at the time of import	SHORT & MEDIUM-TERM
	Introduce temporary flexibilities for in country import testing (e.g. risk-based waivers; accepting receipt on CoA/testing by other parties)	SHORT & MEDIUM-TERM
	Adapted approach to labeling, including e-labelling e.g. Allow digital formats of the PILs in the local language if available and/or develop national portal for approved prescription drug information	SHORT & MEDIUM-TERM
	Acceptance of multi-country packaging including processes to allow unlicensed pack sizes and presentations of the same (identical) medicinal product (to treat COVID-19) on an exceptional case-by-case approach	SHORT TERM
	Promote enhanced market surveillance to prevent the dissemination of and/or early detection of any falsified products	SHORT & MEDIUM-TERM

Research and Development

The scenario of a pandemic health emergency creates a need not only for facilitating clinical research of medicines and vaccines to tackle the novel illness e.g. COVID-19, but also for the continuation and optimization of ongoing research and development (R&D) activities.

Coordination of R&D: Sharing information and finding synergies in R&D efforts is critical in the case of public health emergencies, and PAHO can play a role in this coordination. NRAs should work together from the beginning and accept a reliance approach once a treatment / vaccine is discovered, in order to greatly speed the availability of these products globally. A risk-based approach for reliance supports a more strategic use of resources from NRAs, which should consider completely or partially relying on trusted/reference NRAs processes e.g. clinical trials, scientific advice, alignment on clinical endpoints

Facilitating clinical research: In the context of a public health emergency, there is an urgent need for facilitating clinical research. An increase in the volume of CTA regulatory submissions targeting the same disease can overload NRAs. These are best dealt with via master protocols capable of testing many agents at once, such as the one WHO has proposed for COVID-19. It is important that NRAs are sensitive to this type of approach and encourage fast-tracked approval. Waivers for prior approval or fast-tracked approval for clinical protocols associated with multi-national studies addressing the health emergency e.g. targeting COVID-19 that have gained research and ethics approvals by trusted/reference NRAs can also be a solution. Together with an openness to following decentralized approaches, which can include remote monitoring via digital tools, as patients may not be able to attend regular clinic visits. Waivers should include home delivery of Investigational Drug Product (IDP). Also, temporary rules that support import and control of IDPs with controlled substances and special storage conditions should be considered.

Acceptance of a role for observational data in regulatory decision making: High-quality observational research based on real-world data and real-world evidence collected during the pandemic can be an important complement to the results of randomized clinical trials in providing evidence on the safety and effectiveness of vaccines and treatments for COVID-19. Such research is also critical to understand how exposure to certain medicines can affect the risk or the severity of infection with the virus. Acceptance of the value of real-world evidence in the continuum of the safety and efficacy evidence supplied to NRAs can inform the real-life impact of these medicines. Global real-world data (e.g. collected during emergency/compassionate use as well as post authorization) should be collected as part of the on-going evidence generation plan. In addition to the data collected during traditional clinical trials, NRAs may wish to accept a role for observational data as part of the scientific evidence for initial approval and ongoing benefit/risk assessment.

Table 4: Summary of Research and Development – Challenges and potential approaches to consider

CHALLENGE	POTENTIAL APPROACHES TO CONSIDER WHEN ADDRESSING THESE CHALLENGES	RECOMMENDATIONS FOR IMPLEMENTATION
Clinical research related to COVID-19: High number of requests for NRAs to review	PAHO and NRAs to foster sharing of information and finding synergies in R&D efforts	SHORT TERM
	Fast track scientific advice for relevant drugs and vaccines and/or reliance on scientific advice issued by trusted/reference authorities	SHORT TERM
	Using master protocols capable of testing many agents at once e.g. WHO Solidarity Trial	SHORT TERM

and approve clinical trials	Fast-track or waive prior approval of international clinical protocols targeting COVID-19 that have gained research and ethics approvals by trusted/reference NRAs	SHORT TERM
Inability to carry out clinical trials on site	Openness to following decentralized approaches e.g. Remote monitoring via digital approaches including remote source data verification	SHORT & MEDIUM-TERM
	Delivery of medicine samples at patient home	SHORT & MEDIUM-TERM
	Flexibility in the importation and custom procedures for clinical trial product, avoiding delays in product to patient	SHORT & MEDIUM-TERM
Generate evidence on the safety and effectiveness of vaccines and treatments for COVID-19	Acceptance of a role for observational data in regulatory decision making e.g. high-quality observational research based on real-world data and real-world evidence collected during the pandemic	SHORT & MEDIUM-TERM

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FIFARMA is the Latin American Federation of the Pharmaceutical Industry created in 1962. We represent 14 research-based biopharmaceutical companies and 11 local associations dedicated to discovering and developing innovative, quality and safe health products and services that improve the lives of patients in Latin America and the Caribbean and advocate for patient-centric, sustainable health systems characterized by high regulatory standards and ethical principles.

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Notes

[1] Industry has observed that during health emergencies some countries stop the evaluation of dossiers already submitted and no longer receive new submissions (both registration and post-approval changes) during the pandemic period. While this is a potential route to managing reduced capacity in the immediate crisis, there may be longer term unintended consequences, as any existing 'backlogs' within the system will increase once these regulatory activities resume. Current resources and capacity in the region mean many NRAs will not be able to evaluate these in a timely fashion and important delays in approvals (e.g. post approval changes) may occur. In the longer-term this may lead to potential shortages and limiting new treatment options for patients. This issue will be even more critical for those countries where expedited review is not allowed or the standard timeline for regulatory assessment is lengthy.

[2] Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions, WHO, Annex 9, WHO Technical Report Series, No. 1010, 2018

[3] Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19), Pan American Health Organization, 2020.

[4] Some countries do not allow dual sourcing. Any addition of new manufacturer would constitute a 'New Drug Application'.

[5] In accordance with GMP requirements