A practical overview of requirements for drug registration in Latin America

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Abstract
The regulatory process to obtain marketing authorisations (MAs) for drugs in Latin American (LATAM) countries, despite regional harmonisation efforts, is highly country-specific. Complex and evolving ad-hoc requests from reviewers must be proactively addressed to avoid costly delays or show-stoppers to local product launches. This article offers a practical overview of product registration processes in LATAM, resulting from more than a decade of experience in a biotech company, to ensure successful global regulatory strategy. Although the International Conference on Harmonisation (ICH) Common Technical Document (CTD) can serve as a resource for most local MA applications, it is not necessarily required in its full length. Additionally, a significant amount of mandatory and highly country-specific documentation (related to infrastructure, legal documents, stability studies, labelling, etc) require strategic planning and allocation for successful and timely local approvals. Exhaustive identification of actual requirements can present challenges due to frequent changes in regulations, unclear expectations, etc. Having as much early visibility and command of the LATAM country-specific requirements and health authorities’ (HAs) expectations will help the pharmaceutical industry to improve planning for global MA applications, optimally manage internal expectations, and most importantly give patients in the region faster access to therapies and better quality of life.

Introduction
The LATAM pharmaceuticals market has grown steadily in the past 15 years. It has also been dominated by multinational companies based in Europe and the US that have spread to these “emerging” economies mainly to expand their businesses or to find untreated patients for clinical trials.

This trend has also influenced the evolving growth of the local drug regulations in the LATAM region: with the rapid introduction of high-technology medicines into import, export and distribution networks, it has become critical for each HA to guarantee that the medicines allowed to reach local patients are in compliance with specific standards of quality, safety and efficacy.

With varying levels of sophistication, resources and overall expertise, each LATAM HA has strengthened its health legislation. The region offers a wealth of opportunity for both the pharmaceutical industry and local patients but the variation in the drug registration processes causes time-consuming and costly obstacles for companies.

Based on more than ten years of experience registering drug products in LATAM, this article provides a practical overview of drug registration requirements in the region, with specifics on issues critical to consider for efficient regional regulatory strategies.

The main focus here relates to MAs for prescription drugs (including biologics/biotech). It does not cover the registration processes for devices, biosimilars/generics or clinical trials.

Brief overview of the region
With the exception of Mexico, located in North America, all LATAM countries are situated in either Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela), or the Caribbean (more than 20 countries and territories including Aruba, the Bahamas, Cuba, the Dominican Republic, Haiti, Jamaica, and Trinidad and Tobago). This region has a population of 582.5 million, compared with approximately 734 million in Europe, with 80-85% of the population concentrated in metropolitan areas. LATAM is ethnically and geographically diverse. From a practical perspective, the first language of most Latin Americans is Spanish except for Brazilians, who speak Portuguese. Other languages are spoken (for example, English in Trinidad and Tobago, French in French Guiana, and Dutch in Suriname) but only by a minor fraction of the population. The Spanish language varies markedly between countries, especially the more vernacular or spoken language.

Socioeconomic and demographic factors, like literacy and quality of healthcare, also present with strong variations between countries, and, within countries, between urban and suburban areas. Culturally, the panoply of countries of this region is as varied as their geography, which runs from impressive mountains to coastal lowlands, from tropical rainforest, arid deserts and vast grasslands to cold, windswept Patagonia. This diversity influences the politics and to a certain extent contributes to the HAs’ idiosyncrasies.

General considerations of the drug registration process
Unlike the EU or the Association of Southeast Asian Nations (ASEAN) countries, LATAM drug registration processes are not harmonised. Substantial harmonisation efforts have been ongoing for the past fifteen years, mainly through the initiative of the Pan American Health Organization (PAHO) via the Pan American Network for Drug
Regulatory Harmonization (PANDRH). PANDRH has periodically generated recommendations for a number of key topics (including pharmacovigilance and pharmacoeconomics) to strengthen local HAs and regional regulatory harmonisation. However, in practical terms, every country has its own regulatory requirements. There is no regional “CTD”-like application and each MA application needs to be planned and executed as per the requirements of each country’s HA, thus bringing country-specific challenges to pharmaceutical companies seeking marketing penetration in the region.

To date, there are five national reference authorities in the region, as recognised by PAHO, those from Argentina, Brazil, Colombia, Cuba, and Mexico. Recent attempts at homologation, or allowing the approval from one regional reference authority to facilitate approval in another country, have presented challenges. For example, a homologation process was recently announced for both El Salvador and Ecuador if an approval from the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) is granted. Salvadorean and Ecuadorian experts, however, have confirmed that, from a practical point of view, this is still in the process of implementation until the local HAs issue further regulations related to this initiative. Thus, to date, registration in these countries must be pursued independent of Mexican approval, and according to local requirements.

**Overall drug registration requirements**

It is reasonable to say the bulk of the information needed to build an MA submission in any LATAM country can be obtained working from the ICH CTD. However, most countries require an additional, substantial amount of information that can be challenging to obtain (eg, raw data from the manufacturing or testing process). Dossiers must often also include significant country-specific information (eg, labelling or legal documents). It should not be assumed that local regulations are fully aligned with ICH guidelines. This assumption could create delays or barriers to building fully compliant dossiers.

In many countries, all pharmaceutical products, whether small molecules or biologics/biotech products, are regulated via the same set of regulations or guidelines. Factors such as regional commercial treaties, access to information from reference agencies, and the evolution of countries’ knowledge and expertise in the complexities of manufacturing and quality control of biologics (and especially products produced by DNA-recombinant technology) have triggered a relatively recent wave of regulations for biologics/biotech and other legislation related to more specific patient populations, eg, orphan drugs for patients with rare diseases.

Early identification of documentation or activities needed prior to filing, and optimal allocation of the time, cost and resources for these issues, are essential for the success of the global regulatory strategy.

General facts regarding the MA application process in some key countries of the region are included in Table 1. Examples of the complexity of local MA applications in LATAM in terms of either content or process, and the associated challenges, are detailed below.

**Local infrastructure needed for filing.** Even before planning a product registration in LATAM, companies need to research the country-specific mandates related to the entity legally allowed to file an MA application. In many countries, the applicant must hold an authorisation or certification in order to eventually become a marketing authorisation holder (MAH), as granted by a relevant local authority or agency(ies). In Argentina, for example, only a locally authorised laboratory, with a licensed pharmacist, can file a registration dossier. Getting a local presence authorised in some countries can be a highly bureaucratic and long process with several time-consuming steps.

Partnering with a locally authorised company (such as distributors, laboratories, etc, or other logistics-related associations, like warehouses), instead of establishing a local entity suffices in certain countries but attention must be given to the associated activities required to be in place prior to the MA application, such as due diligence and agreements. Alternatively, in some countries in Central America, a country native expert with a valid power of attorney is enough to proceed with a submission.

Local dossiers usually require proof of the required local infrastructure to register and eventually market a product: local authorisation(s), power of attorney, letter of authorisation, contracts, business and/or quality agreements, etc.

Approvals of reference agency (EMA/US FDA). To a certain extent, and regardless of the evolution of local registration requirements, in many cases each local registration process can still be perceived as a “validation” of those from reference agencies. The European Medicines Agency (EMA) and the US FDA are still “the” main reference authorities not only for local approval but also for issues like labelling.

In order to prove a reference agency’s approval, most countries rely on the Certificate of Medicinal Product (CMP), issued by the EMA, or a Certificate of Pharmaceutical Product (CPP) from the US FDA or country of origin, as applicable. Brazil accepts a dossier without a CMP/CPP for submission but it is needed before local approval (recently, however, the lack of CMP/CPP has been used as a reason for rejection). Mexico accepts dossiers without a CMP/CPP under certain conditions and as long as clinical data in Mexican patients is available.

Most other LATAM countries will not accept an MA application without a CMP/CPP.

Refer to Table 1 for more detail on this topic for key LATAM countries.

- **Quality (chemistry, manufacturing and controls (CMC)) requirements.** Depending on the country, dossiers usually require a significant CMC/Quality section. Examples of required quality documentation not found already in the source CTD are chromatograms or any other type of raw data for release testing or in-process controls, full standard operating procedures (SOPs) from diverse parts of the manufacturing process or from the release testings of Drug Substance (DS) and Drug Product (DP), validations of the manufacturing process or the release testing, or batch records.

In the case of stability data, lack of country-specific required data is a critical show-stopper. Examples of deficiencies that some agencies identify include: inadequate quantity of data, incomplete studies, lack of studies under the country’s climatic zone conditions, omission of start and end date of studies, omission of relative humidity, or lack of stability under stress conditions for biologics/biotech products. Many countries, especially in Central America, require the data from these stability studies to be formatted under country-specific guidelines and duly signed by the responsible person in charge of studies or the manufacturing facility. Some detail on this topic for key countries in LATAM is listed in Table 1.

It is not unusual that HAs, like the Peruvian General Directorate of Medicines, Supplies and Drugs (DIGEMID), come back to MA
applicants with requests to tailor or to qualify statements of DP specifications, thus creating different “flavours” for the certificates of analysis (COAs) in the region.

Another frequent requirement is good manufacturing practice (GMP) certificates from reference agencies for the facilities involved in the product manufacturing process; and in their absence, some countries require company establishment licences.

Brazil requires inspections of the manufacturing sites by the National Agency of Sanitary Surveillance (ANVISA), for product approval. Thus, an inspection request, which is a separate application from the MA application, needs to be built from site master files (SMFs) and other manufacturing-site-specific documentation, and filed prior to the MA application.

Factors such as timing of the submission of the inspection request(s) in comparison with the MA application, inspectors’ availability, and the compliance of sites with ANVISA’s GMP legislation could create delays and mean the difference between acceptance and rejection of MA applications.

**Nonclinical and clinical requirements.** Some countries, for example Argentina, do not need the submission of nonclinical or clinical data if the product is approved by a reference agency. Most other countries, such as Brazil, require safety and efficacy information. Some HAs accept summaries and some, like that of Venezuela, require the full set of clinical data (full study reports), and some require that it be fully translated. More recently, countries such as Argentina and Mexico request risk management plans (RMPs) and pharmacovigilance plans to further ensure proper follow-up of patients once the product is approved locally.

In some countries, such as Venezuela, the HAs might also request the actual scientific articles where the dossier information was published, if available.

**Legal or other ad-hoc documentation.** In addition to necessary documentation related to reference agencies’ approvals and GMP compliance, and that related to local legal entities, some countries (such as Mexico) require local patent and trademark certificates, which require another application in-country in advance of the MA application.

Other examples of ad-hoc requests that are often mandatory for LATAM dossiers include letters committing to maintain a cold chain (for refrigerated products), waste disposal statements or procedures, and requests for data protection (countries in Central America and Caribbean require this type of documentation).

**Local labelling.** Usually, the MA application requires the inclusion of the proposed local labelling (inserts, patient information, vial label, etc, as applicable). In many cases, a “mock-up” of the proposed labelling must be included.

As much as a company would prefer to harmonise labelling for the region, this intention is often challenged by the diversity of local regulations and also by independent reviews from each HA. Thus it is extremely difficult to implement harmonised labelling. Some countries, for example Peru, only accept indications which are aligned with those from another reference agency (for example, the FDA and EMA).

Agencies often require the labelling to include local information (registration number, manufacturer, licensed pharmacist, distributor, packer, etc). Once approved, countries may also require implementation of specifics such as local barcodes, traceability devices (Argentina and Brazil), and braille (Brazil). Refer to Table 1 for other details on this topic for key LATAM countries.

**Samples (registration testing) and/or repetition of release testing locally.** HAs might request samples at or around the time of filing (for example, in Venezuela and Chile). Since the HAs often re-test the DP samples against company’s release testing, reference standards and reagents can also be required (such as in Panama). Import licences and clearance from Customs also need to be considered and effectively executed, especially when the dossier and samples must be filed together.

Countries like Argentina and Brazil require the repetition of release product testing at the local level once a product is approved and during commercialisation (in-country testing). In Brazil, this requirement has been waived for biologics, as long as the product is shipped with temperature monitoring devices. In some cases, this in-country testing can be performed either by a partner (distributor or local authorised laboratory) or by a laboratory certified by the local agency (such as for Venezuela and Mexico). In Mexico, in addition to local testing, companies must repeat local stability studies for the DP.

Refer to Table 1 for other details on this topic for key LATAM countries.

**Compilation (translations) and submission.** In the compilation and submission process, one must look for stumbling blocks in submission language, format, appointments with HAs, and additional requirements for special cases.

Each country’s registration dossier, in addition to proof of fee(s) payment, usually includes a country-specific local form(s). Although some countries accept a few sections in English, as a rule all MA applications need to be fully translated into the country’s language before submission. It is therefore essential to budget for translation time and cost in global strategies.

Many of the legal and ad-hoc documents (CMP/CPP, GMP, and contracts, for example) need to be notarised, and often even further apostilled (for Hague convention countries) or consularised (authenticated by the consulate or embassy of the country where the dossier will be filed, located in the country and jurisdiction of origin of the document).

Chile has recently implemented a required electronic submission process. Argentina is also starting to use this modality, while Brazil, Colombia, and Peru accept it but do not mandate it. Other countries still require submission on paper.

For some countries, eg, Venezuela and Costa Rica, the applicant must schedule a meeting with the agency to file an application. In Mexico, for new molecules, the applicant needs to present the candidate product to the “New Molecules Committee” to obtain agreement with the local HA on the local MA application’s strategy, such as implementation of local pharmacovigilance plans.

**Review process.** Review times are highly variable not only between countries but also within each country based on the product’s characteristics. In general, review times could range from three months (for example, in Paraguay and Ecuador) to two to three years (for example, in Venezuela). It is challenging to predict accurate review times, although some agencies offer the chance to monitor the review process electronically, to help applicants anticipate questions and expected approval.

Brazil’s ANVISA is a highly sophisticated agency. PAHO’s recognised regional reference HA, with the most frequent updates to regulations and reinforcement of implementation of legislation. To reduce recent delays in local MA application review timelines, ANVISA has announced
### Requirements/Considerations

<table>
<thead>
<tr>
<th>Requirements/Considerations</th>
<th>Argentina (ANMAT)</th>
<th>Brazil (ANVISA)</th>
<th>Chile (ISP)</th>
<th>Colombia (INVIMA)</th>
<th>Mexico (COFEPRIS)</th>
<th>Peru (DIGEMID)</th>
<th>Venezuela (INHRR)</th>
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<tbody>
<tr>
<td><strong>CMP/CPP required for submission?</strong></td>
<td>Yes, or proof of commercialisation from approved reference market. (A full dossier must be submitted if no CMP/CPP is available).</td>
<td>No. Not needed for submission but it is required for local approval.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, but can be waived under certain conditions and if clinical data from local patients are available.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Are biologics/biotech products regulated as drugs?</strong></td>
<td>No, recent biologics/biotech regulation was implemented and requires a more complex dossier.</td>
<td>No, recent biologics/biotech products regulation was implemented.</td>
<td>No, drugs and biologics/biotech have separate requirements.</td>
<td>Yes, but proposal for the regulation of biologics/biotech is under consideration (laws in draft).</td>
<td>No, biologics/biotech legislation was recently implemented.</td>
<td>Yes, but proposal for the regulation of biologics/biotech is under consideration (more complex, changing from current 4 to 12 requirements).</td>
<td>No, there are separate requirements for drugs and biologics/biotech.</td>
</tr>
<tr>
<td><strong>Orphan drug legislation in place?</strong></td>
<td>Recent regulations (August 2012): complex dossier, pharmacovigilance (PV) plans, monitoring of efficacy, effectiveness and safety plans, labelling requirements, not clear advantages yet.</td>
<td>Decreases 2577/2006, 768/2006, RDC 28/2007, RDC16/2008: in theory allows for priority review – ongoing efforts to issue further new legislation on orphan drugs registration process.</td>
<td>No regulations exist for orphan drugs to date (recent legislation was revoked and to date there is no indication if it will be re-issued).</td>
<td>Law 1392 of 2010 and Law 1438 of 2011; orphan designation application process is not yet defined.</td>
<td>Legal definition for orphan drugs was published in the Official Gazette in January 2012 incorporating article 224 Bis into the General Health Law – further regulations with details on dossier requirements, etc, currently in draft form (March 2013).</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Stability studies</strong></td>
<td>Climatic zone: Local market: Zone II, Zone IV is also accepted.</td>
<td>Climatic zone: Primarily IV (30°C ± 2°C/75% ± 5% relative humidity (RH)). Stress studies for biologic/biotech (possible exposure of the product outside recommended conservation care should be evaluated, such as high temperatures and/or freezing).</td>
<td>Climatic zone: Primarily I and II, it is accepted III and IV for exportation if they fulfil the other requirements.</td>
<td>Climatic zone: Zone IVa, (Zone IVb is also acceptable).</td>
<td>Climatic zone: Primary Zone II (Zone III and IV may be accepted). Norm NOM-073-SSA1-2005: 30°C ± 2°C/65% ± 5% RH.</td>
<td>Climatic zone: Mainly IVa.</td>
<td>Climatic zone: Mainly IVb.</td>
</tr>
</tbody>
</table>

Table 1: Key requirements and considerations for marketing authorisation applications in selected LATAM countries.
<table>
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<tr>
<th>Requirements/Considerations</th>
<th>Argentina (ANMAT)</th>
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<th>Venezuela (INHRR)</th>
</tr>
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<tbody>
<tr>
<td><strong>Other critical and recent issues</strong></td>
<td>New regulations on PV, risk management plans (RMPs), biologics registration.</td>
<td>Inspection request(s) of manufacturing facilities must be filed before MA filing. For biologics, provide copy of GMP issued by ANVISA for all manufacturers of drug substance (DS), drug product (DP) in bulk, DP in primary packaging, DP, diluent and adjuvant. Current ongoing updates (drafts) to legislation and other initiatives, especially re: labelling, traceability, review time, labelling updates, annual reports, etc.</td>
<td>New proposal for GMP guidelines. New proposal for Good Storage and Distribution Practices guidelines. Samples required with MA submission.</td>
<td>MA application occurs in two consecutive applications: first, safety and efficacy (labelling), then second, technical, from which an MA approval is obtained.</td>
<td>Reference agency in the region. Other countries (eg, Ecuador) could base local approval on Mexican one (still in process of implementation). Current ongoing updates, especially re: technical content of dossier, labelling, renewals and post-approval changes, PV plans.</td>
<td>Issues with requests for detailed DP specifications, labelling issues, etc.</td>
<td>Complex application, samples needed with submissions</td>
</tr>
<tr>
<td><strong>Local testing</strong></td>
<td>Repetition of release testing during commercialisation.</td>
<td>Repetition of release testing during commercialisation for small molecules. (Biologics waived but product needs to be shipped with temperature monitors).</td>
<td>Repetition of release testing during commercialisation.</td>
<td>Not required.</td>
<td>Repetition of release and stability testing during commercialisation.</td>
<td>Not required.</td>
<td>Analysis of first commercial batch after MA approval currently under discussion.</td>
</tr>
<tr>
<td><strong>Labelling requirements</strong></td>
<td>In Spanish as per local regulations. Mock-ups required for submission. Local registration number and pharmacist details. Recent implementation of traceability codes. HA recently started to request voluntary inclusion of patient leaflet (while keeping prescription insert).</td>
<td>In Portuguese as per local regulations. Mock-ups required for submission. Local registration and pharmacist information. Red stripe around box for medicines sold under medical prescription. Pursuing serialised two-dimensional codes.</td>
<td>In Spanish as per local regulations. Mock-ups required for submission. Local registration and pharmacist information.</td>
<td>In Spanish as per Mexican norm. Local registration, pharmacist, distributor. (For orphan drugs, labelling from country of origin is currently allowed).</td>
<td>In Spanish as per local regulations. Mock-ups required for submission. Local registration and pharmacist information.</td>
<td>In Spanish as per local regulations. Local registration and pharmacist information.</td>
<td></td>
</tr>
<tr>
<td><strong>Electronic submission?</strong></td>
<td>No, but HA is starting to implement (already in place for locally manufactured products).</td>
<td>Available</td>
<td>Yes (true electronic submission).</td>
<td>Available; otherwise paper.</td>
<td>No</td>
<td>Yes</td>
<td>Paper and electronic files.</td>
</tr>
<tr>
<td><strong>Review time</strong></td>
<td>6–9 months (Questions might come 3 months after submission).</td>
<td>12–18 months (Questions might come ~5–6 months after submission). ~12 months for orphan drugs.</td>
<td>6–12 months</td>
<td>~12 months</td>
<td>12–18 months (Questions might come ~5–6 months after submission). ~6 months for orphan drugs.</td>
<td>~12 months</td>
<td>18–24 months</td>
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</table>

*Review times are highly variable and unpredictable and will depend on product characteristic (biologic vs small molecule, if orphan drug, etc.), local agency resources, reviewer’s perspective, number of rounds of questions from agency and speed of answers from applicant, if deadline to reply is not specified by agency.

Note: Information is subject to change and is based on current regulations and recent experience with biotech and small molecules, and for marketing applications of products already approved by EMA or FDA.9-13
its intention to expedite the drug approval process by 40% by adopting new measures that include an electronic registration system.¹⁶

**Conclusions**

The LATAM region does not have a centralised or harmonised procedure for drug registration. There are critical differences between countries in the region. Moreover, most countries require additional documentation that is not part of Modules 2–5 of the CTD, some of which might also be challenging to obtain. Table 2 lists the primary challenges observed when working in the LATAM drug registration processes and some key recommendation for success in the region. Knowledge of the drug registration processes and submission content for each LATAM country is essential for the effective planning and execution of global regulatory strategy.

Engaging regulatory professionals with expertise regarding the region early in the development phase of a candidate product is crucial. Experts can be internal or external to the company but must be, or have strategic partnerships with, reliable regulatory professionals on the ground who are aware of the practical regulatory nuances and expectations from HAs, and who keep up-to-date with the changes to the regulatory environment in the region, to avoid delays or show-stoppers to the MA applications.

Although not essential, there is an invaluable benefit if a regulatory affairs expert is fluent in the country’s language and cultural nuances in addition to having robust expertise in the local regulatory framework and practices.

Local authorities in the region are eagerly learning from each other and from other international agencies. There is rapid acceptance of new technologies and paradigms but above all, there is a fundamental driver: genuine concern for access to new therapies for local patients.

**Table 2: Overall recommendations for successful global regulatory strategy including LATAM countries.**

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Regulatory differences across the region</td>
<td>⚫ Master the requirements or partner with regulatory professionals with knowledge of each country’s regulatory process</td>
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<tr>
<td></td>
<td>⚫ Work within each set of requirements and associated timelines for each country where marketing authorisation is pursued</td>
</tr>
<tr>
<td>Language and cultural barriers</td>
<td>⚫ Awareness of these factors is critical for success in an environment often relying on relationships and negotiations where there are regulatory ‘grey areas’</td>
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<tr>
<td></td>
<td>⚫ Work with reliable, knowledgeable experts, either at local or corporate headquarters, and either internal or via contracting parties</td>
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<tr>
<td>Internal team’s challenges</td>
<td>⚫ Engage regulatory affairs teams with knowledge of registration processes in LATAM early in the planning of global strategy</td>
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<tr>
<td></td>
<td>⚫ Throughout the planning and execution process, effectively manage expectations with ex-registry teams who might question unusual requests deviating from known EMA/FDA requirements or budget-consuming requisites: communication is key</td>
</tr>
<tr>
<td>Constant change to regulations in the region</td>
<td>⚫ Monitor frequently for updates to requirements or other regulatory developments.</td>
</tr>
</tbody>
</table>

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8. COFEPRIS. ‘El Salvador y Ecuador, primeros países en reconocer registros de medicamentos de México’, Press release from COFEPRIS, GoMx, 2012. http://www.encuentracob.mx/resultsAPF.html?q=E%20SALVADOR%20y%20ECUADOR%20PRIMEROS%20PA%20RECONOCER%20REGISTROS%20DE%20MEDICAMENTOS%20DE%20M%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20%20...