Medical Device Regulation in Latin America

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Market Overview

Mexico

Colombia

Peru

Brazil
Brazil

GDP per capita: $15,500
Health Expenditure: 8.3% of GDP
Median age: 32
Life Expectancy: 74 years
Topics

• Overview of Regulatory Framework
  - ANVISA and Medical Device Regulations
  - Classification and Grouping

• In-Country Representation
• QMS Requirements
• Registration Requirements
• Post-Approval
  - Modifications and Renewals
  - Vigilance
Overview of Regulatory Framework

- ANVISA and Medical Device Regulations
- Classification and Grouping
National Health Surveillance Agency (ANVISA)

- **Agência Nacional de Vigilância Sanitária (ANVISA)**
- ANVISA is a division of the Brazil Ministry of Health
- Regulates medical devices and IVDs
- Health Surveillance Standards (Law No. 6360/1976) and Health Surveillance Decree (No. 8077/2013) – main medical device laws
What is a medical device?

Definition of a Medical Device from Annex I, section 13, of Resolution RDC No. 185/2001:

Health product, such as equipment, apparatus, material, item or system with a medical, dental, or laboratory use or application for prevention, diagnosis, treatment, rehabilitation and that does not use contraception and pharmacological, immunological or metabolic to perform the main function in humans, but can be assisted in its duties by such means.
Medical Device Classification

- **Four tier** classification system based on risk
  - Class I and II devices, cadastro (low risk)
  - Class III and IV devices, registro (high risk)
- Classification system similar to EU
  - Classification Rules included in RDC 185/2001
- ANVISA maintains a list of products not regulated as medical devices
  - E.g., wheelchairs, toothbrush, etc.
IVD Classification

• Rule system based on Global Harmonization Task Force (GHTF) guidelines
• Class I-IV
  - Class I and II IVDs, cadastro (low risk)
  - Class III and IV IVDs, registro (high risk)
• ANVISA has a classification database for common IVDs
  http://www.anvisa.gov.br/datavisa/NomesTecnicosGGTPS/Consulta_inVitro.asp?ok=1
Grouping Medical Devices

ANVISA categorizes products into three main types:

**Materials**
Non-active medical devices, e.g., catheters, stents

**Equipment**
Health equipment, mainly active products

**IVD**
In Vitro Diagnostics
Grouping Medical Devices

• ANVISA has specific grouping guidelines based on type of device, which do not follow European or US FDA guidelines
  • There are also separate guidance documents for specific products. Example: orthopedic implants
• Different types of devices (e.g., materials and equipment) cannot be grouped together
• ANVISA reviewers are split by category
  • One set of reviewers for “material” products, and another for “equipment” products
In-Country Representation
Brazil Registration Holder (BRH)

- All manufacturers without a Brazilian entity must appoint an in-country representative
- BRH must meet criteria to submit and hold registrations:
  - Licensing requirements, e.g., Operating permit (AFE) from ANVISA, sanitary license from local VISA
  - Personnel requirements, e.g., full-time Technical Responsible (licensed pharmacist, nurse, engineer, etc.)
- BRH and Technical Responsible on the label
BRH Responsibilities

- BRH submits and controls device approval
  - BRH must authorize each importation shipped under its registration number via an Authorization Letter
  - BRH tied to other related certifications such as Brazil Good Manufacturing Practice (BGMP) certification
- BRH is responsible for vigilance activities, and maintaining records/files of technical complaints
- BRH subject to ANVISA audits
  - Must maintain complaint warehouse and procedures. Example: post-market surveillance
Advantages of using 3rd party instead of a distributor

- Protect Confidential Information
- Stay up-to-date on Regulatory Changes
- Avoid a Conflict of Interest
- No interest in commercial activities; focused on regulatory affairs and the interests of the manufacturer
Emergo’s BRH Extra! Client Site

• Helpful guides:
  - Distributor Requirements
  - Labeling Guide for Equipment and Material
  - Renewals Guide
  - INMETRO Certification Guide

• Complimentary tools:
  - Modification Process Flowchart
  - Importation Flowchart
  - 10+ available checklists

• 100+ FAQs

• Brazil regulatory updates
QMS Requirements
Brazil Good Manufacturing Practices (B-GMP)

- RDC 16/2013
  - Similar, but not equivalent, to ISO 13485
  - All devices must be compliant, but only Class III/IV (registro) sites require B-GMP certification
    - Inspection per applicable manufacturing facility
    - 3+ year wait time for inspection
    - Technically B-GMP certificate required to obtain approval for Class III/IV products
- B-GMP certificates valid for two years
- ANVISA fee: BRL$72,806 (~USD$22,000/Euro €18,000)
B-GMP Auditing Process

- Provide B-GMP application documentation
- ANVISA will review application to determine onsite or offsite inspection
- Onsite audits are scheduled for three to five days, depending on the size of the company and the number of products manufactured at the facility
- Audit is mainly focused on the product and safety
  - Design control and verification, risk management, and customer complaint process
- Manufacturers have 120 days to address findings (“requirements”) after issuance of audit report
Don’t want to wait 3+ years for an inspection?

OPTION 1: Medical Device Single Audit Program (MDSAP)
- Conduct single audit to QMS requirements of Australia, Brazil, Canada, Japan, and/or USA
- Must use accredited Auditing Organizations (AO)
- Must still pay ANVISA B-GMP fee
- *With new (Q4 2017) GMP regulation of possible offsite audits, not as beneficial as previously anticipated*

OPTION 2: Sue ANVISA directly to expedite process
- Typically inspected within nine months
- Must pay law firm to file suit

OPTION 3: File under industry group joint lawsuits
- ABIMED members sued ANVISA due to long wait time
- Members can submit registration application six months from B-GMP inspection request date, with proof of other QMS certification
Registration Requirements
Cadastro: Class I and II

• Does not require ANVISA B-GMP inspection
• Application + Technical Dossier
  - Separate from the “cadastro” registration application
  - BRH is required to maintain TD; ANVISA can request TD during audit of BRH
  - More extensive requirements than application, e.g., Biocompatibility and usability/human factors data

<table>
<thead>
<tr>
<th>Fee:</th>
<th>~US$400</th>
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<tbody>
<tr>
<td>Timeline:</td>
<td>2-4 Months</td>
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</table>
Technical Dossier (TD) Requirement

- Required for all new cadastro applications
  - Devices registered before August 2016 have a transition period
- Separate from, and in addition to, the cadastro application
  - More extensive requirements than application, e.g., Biocompatibility and usability/human factors data
  - Follows IMDRF Table of Contents format
- Except for Class II IVDs, TD is not submitted to ANVISA
- BRH is required to maintain TD; ANVISA can request it during an audit of BRH
Registro: Class III and IV

- Substantial technical information
- Clinical data from completed studies for certain devices (e.g., long-term implantable)
- Requires B-GMP certificate
- Valid for 10 years

<table>
<thead>
<tr>
<th>Fee:</th>
<th>~US$1,770-$2,400</th>
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<tbody>
<tr>
<td>Timeline:</td>
<td>2-4 Months + 4 years for B-GMP</td>
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</table>
INMETRO Certification

• Required for most electro-medical devices
  • And other specific products, e.g., hypodermic needles, breast implants, condoms

• All classes could require INMETRO
• INMETRO Certificate requires BRH
• Certificate must be included in ANVISA device application
INMETRO Testing & Inspection

• Test reports *must* be less than two years old – otherwise, some retesting mandatory
• Inspection of manufacturing facility(ies)
• Inspection of BRH and Importers
## INMETRO Time and Fees

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Validity</strong></td>
<td>Five years, with annual on-site audits</td>
</tr>
<tr>
<td><strong>Fees</strong></td>
<td>Approximately $6,000 - $10,000 per device</td>
</tr>
<tr>
<td></td>
<td>Approximately €5000 - €8100 per device</td>
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<tr>
<td><strong>Timeline</strong></td>
<td>About 3-6 months</td>
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</table>
Additional Certifications

**ANATEL Certification**
- Devices incorporating wireless or Bluetooth functionality
- In-country testing always required

**MTE Certification**
- Protective Products, e.g., protective goggles

**INCQS Certification**
- Blood bags and blood screening IVDs used in blood banks
Post-Approval

- Modifications and Renewals
- Vigilance
Modifications

- Product, IFU/label, and company related changes must be notified to ANVISA - E.g., intended use, shelf life, manufacturer name change, etc.

<table>
<thead>
<tr>
<th></th>
<th>Class I/II</th>
<th>Class III/IV</th>
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<tbody>
<tr>
<td>Submission</td>
<td>Multiple changes can be submitted within a single request</td>
<td>Separate submission per change</td>
</tr>
<tr>
<td>Fee</td>
<td>$0</td>
<td>~US $400</td>
</tr>
<tr>
<td>Review Timeline</td>
<td>~1-4 Months</td>
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</table>
Transferring Registrations

• RDC 102/2016 effective December 2016
• Transfer possible with the full cooperation of the existing BRH
  • BRH must sign a Transfer Declaration, and submit a cancellation request
• New registration number issued to new BRH
• Related B-GMP and INMETRO certificates must also be transferred

Fee:
• Cadastro: $0
• Registro ~$400/€325

Timeframe:
• Transfer approved in 2-3 months
• Transfer effective 90 days after the application is approved
Renewals

- Must submit within 6-12 months before expiration - applications submitted outside this period will be rejected
- No updates to the manufacturer or product information can be included
- Renewals must include upgrades to incorporate regulation changes

Fee (Class III and IV): ~US$1,600 - $5,000

Review Timeframe: 3-4 Months

Validity (Class III and IV): 10 Years

Class I/II device registrations do not expire
Vigilance

• Post market surveillance system resembles European guidance on vigilance
• BRH is responsible for:
  - Informing ANVISA of events by submitting a form on their website
  - Maintaining records/files of technical complaints
• ANVISA is highly vigilant, so manufacturers must be aware of requirements and reporting
  - E.g., Serious Adverse Events (SAE) must be notified to ANVISA in 10 days
Emergo Brazil: Qualifications and Experience

- Two Brazil locations: Brasília and São Paulo
- Established 2010, through acquisition of an existing consulting firm
- Large experienced team
  - ~20 full-time employees
  - All consultants are bilingual in Portuguese and English
- Director of RA/QA teaches post-grad Regulatory Affairs courses at two universities
- Our Technical Responsible has:
  - Pharmacy and biochemistry degrees
  - Master’s degree in Research, Quality Control, and Development of Drugs
  - MBA with a focus on Regulatory Affairs (emphasis on Medical Devices)
Emergo is reputable with deep connections in Brazil’s medical device industry

• 449+ ANVISA approvals: We have the experience!
  - Professional project management
  - Established procedures under RDC 16/2013
• ABIMED membership
• Independent representation

We can act as your single regulatory contact in Brazil and 20+ countries worldwide.
Meet the Emergo Brazil Consultants
Colombia

GDP per capita: $14,500
Health Expenditure: 7.2% of GDP
Median Age 30
Life Expectancy: 75.9 years
Topics

• Overview of Regulatory Framework
• Regulatory Process
• In-Country Representation
• Post-Approval
Overview of Regulatory Framework
The National Food and Drug Surveillance Institute (INVIMA)

- INVIMA (El Instituto Nacional de Vigilancia de Medicamentos y Alimentos)
- Decree 4725/2005, and amendments
- Home-country approval or approval in AU, CA, EU, JP, or USA required
Medical Device and IVD Classification

Medical devices
- Four-tiered, risk-based system – based on MDD
- 18 Classification Rules
- Classes I, IIa, IIb & III – almost always align with Europe
- “Non-Controlled” (Class I/IIa) and “Controlled” (Class IIb/III)

IVDs
- Three-tiered risk-based
- Classes I, II & III
Regulatory Process
Regulatory Process: Non-Controlled Devices (Class I/IIa)

- Submit registration dossier (including technical information, test reports, risk analysis, QMS certificate, etc.)
- Immediate acceptance, can start importing
- INVIMA will still review application; could request additional information
  ✓ 90 days response time or registration could be revoked
Regulatory Process: Controlled Devices (Class IIb/III)

- Submit registration dossier (including technical information, test reports, risk analysis, clinical data, QMS certificate, etc.)
- Full technical review and approval required prior to import
- Official review time 90 calendar days; actual review timeline within 6 months
In-Country Representation
In-Country Representation

Need to appoint a representative in Colombia to manage registration with INVIMA

- **Option 1:** Issue Power of Attorney (PoA) to a lawyer, or “Legal Representative”
  - Manufacturer can “own” and control their registration through their Legal Representative

- **Option 2:** Issue authorization to process the application to a certified importer
  - Distributor may list themselves as “owner” of the registration – manufacturer loses control

If you register through Legal Rep, must identify licensed importer on registration – can’t submit without one!
Post-Approval
Modifications

INVIMA allows modifications including:

✓ Changing the registration owner
✓ Adding a manufacturer
✓ Product name change
✓ Packaging/labeling change
✓ Adding a new importer, and more.

Information required depends on change

Official review time is 30 business days, actual timeframe can be longer
Renewals and Validity

- Registrations valid 10 years
- Apply for renewal 3 months prior to expiration
- Same documentation required as new registration
- Class I/IIa, automatically approved
- Class IIb/III: approval time is 2 months
  - If renewal was submitted in time, manufacturer can import past certificate’s expiration, if INVIMA has not issued a response

Manufacturers must import within first 3 years of initial approval, or INVIMA will cancel the registration.
Mexico

GDP per capita: $19,500
Health Expenditure: 6.3% of GDP
Median Age: 28.3 years
Life Expectancy: 76.1 years
Mexico: Regulatory Overview

- **Overview of Regulatory Framework**
  - COFEPRIS
  - Medical Device and IVD Regulations

- **Registration Routes**
  - Standard Process
  - Equivalency Process

- **In-Country Representation**
- **Post-Approval**
Overview of Regulatory Framework
The Federal Commission for the Protection against Sanitary Risk (COFEPRIS)

- La Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)
- Division of the Ministry of Health
- Oversight of MDs and IVDs through sanitary regulation, Ley General de Salud (General Health Law)
What is considered a medical device?

Substance, mixture of substances, material, device or instrument (including computer program necessary for proper use or application); used alone or in combination with others in the diagnosis, monitoring or prevention of disease in humans; or aids in the treatment of the same and of disabilities, such as those employed in the replacement, correction, restoration or modification of the anatomy or human physiological processes.
## Classification System

### Level of risk to patient or user

**Update: Apr. 17, 2018**

<table>
<thead>
<tr>
<th>CLASS I</th>
<th>CLASS II</th>
<th>CLASS III</th>
</tr>
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<tbody>
<tr>
<td>Low Risk</td>
<td>Class I</td>
<td>Class II</td>
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</table>

| Very low-risk | Products well-known | Products well-known | High risk |
| Require a simple registration | Proven safety and effectiveness | May have variations in material with which they are made or in their concentrations | Typically novel products |
| Generally, not introduced into the body | Generally, not introduced into the body | Remain in the body < 30 days | Remain in body > 30 days |
Medical Device and IVD Regulations

- Update: Apr. 17, 2018
- COFEPRIS classification system covers MDs and IVDs
- Classification Criteria similar to EU MDD 93/42/EEC:
  - Now 23 classification rules *(Formerly 20 classification rules)*
  - New IVD Rules 18 – 21. *(Formerly all IVDs fell under rule 19).*
  - New rule 23 for Low-risk medical devices.
- List of non-regulated and “Low Risk” devices
  - Non-regulated: Hospital beds, scales, etc.
  - Low Risk: bandages, dressings; some physical therapy equipment (“exercisers”)
- Certain products require in-country testing in Mexico prior to submitting registration to COFEPRIS16
Grouping Requirements

• Grouping for Mexico is more challenging than many other markets

• Must consider:
  ✓ COFEPRIS Grouping Criteria – general, not a law/regulation
  ✓ How similar products are approved
  ✓ How the products will be packaged and sold
  ✓ Experience of what we know COFEPRIS expects

• Stricter than Europe on certain criteria, e.g.: manufacturing facilities, how the products are packaged and sold, and more.
Registration Routes
Registration Routes

- Multiple Routes to Registration:
  1. Standard Process
  2. Standard Process with Third Party Reviewer
  3. Equivalency Process
     - US FDA
     - Health Canada
     - Japan

- Routes affect cost/time more than classification
- COFEPRIS fees the same for all routes: ~ US $500-$1,000 per registration
Standard Registration Route

- Requires home country approval, plus proof of audited QMS (e.g., ISO 13485)
- Robust dossier, including full test reports translated into Spanish
- Submit application to COFEPRIS for technical review and final approval
- Longest approval timelines
  - Can be 8-12 months for first response, no transparency
  - Total actual approval timelines vary widely
Standard Registration Route with Third Party Reviewer (TPR)

• Who are TPRs?
  - Independent, commercial entities accredited by COFEPRIS to review and “pre-approve” registrations
  - Mexican companies, not international Notified Bodies/Registrars

• Currently 15+ TPRs
• Fees and deliverables vary by TPR
• TPR can only review Standard Process registrations
Standard Registration Route with TPR

• Most expensive route to market, but also fastest
• TPR fees vary by TPR
  ✓ US $3,000-$6,000 on average per registration, depending on device classification and TPR
• Three-six month approval timeframe
• Better transparency
• Local representative (Mexico Registration Holder (MRH)), must contract with TPR directly
• TPR recommends approval; only COFEPRIS issues the approval certificate
US FDA Equivalency Route

- Class I, II, III devices eligible
- 12+ month approval timeline
- Less robust dossier than Standard Route
  - ✓ Do not require translated test reports, only summaries
- Must be able to provide:
  - ✓ FDA Establishment Inspection Report (EIR) or ISO 13485 cert (ONLY if FDA has not inspected — COFEPRIS will verify)
  - ✓ Certificate to Foreign Government (CFG)
  - ✓ Class II, III devices: history of adverse events
  - ✓ Proof of FDA Listing, Clearance, Approval
Health Canada Equivalency Route

- Limited to Class II, III, and IV devices (Class I not eligible)
- 12+ month approval timeline
- Equivalency registrations do not require translated test reports, only summaries
- Must be able to provide:
  - Class II-IV Medical Device License (MDL)
  - ISO 13485 Certificate with CMDCAS
  - Standards Council of Canada accreditation to Registrar
  - ISO 17021 certificate of the Registrar
Japan Equivalency Route

- Fastest route to approval (1-3 months)
- Limited to Class II-IV products (no Class I)
- Must be able to provide:
  - Certificate of Free Sale
  - Certificate of Export from Japan
  - Copy of Certification or Approval
In-Country Representation
Mexican Registration Holder (MRH)

Requirements to submit and hold medical device registrations:

- Must be legal entity established in Mexico
- Have a compliant warehouse and maintain a Warehouse Operation Notice (Aviso de Funcionamiento)
- Employ a Health Quality Manager
- Comply with local QMS requirements, NOM 241

More than one company can submit COFEPRIS registrations for the same device; however, companies need to submit a new registration including all costs and timeframes.
Post-Approval
Import Permits

• Certain products require an import permit
  - Most Class III devices
  - Certain Class II devices, e.g., catheters
  - Products that require in-country testing, e.g., x-ray/radiation equipment
• Product’s specific Harmonized System Code determines if import permit is required
• Issued with a set validity date (180 days) & for a certain number of devices
  - Validity can be extended for another 180 days, given number of devices allotted by the original permit has not been imported
• Fees: ~US $100 for new import permit, ~ US $15 for import permit extension
• Timeline: 8 weeks
Modifications

- Two types of modifications:
  - Administrative – e.g., add/change distributor, company name change, etc.
  - Approval timeline (regardless of route): 1-6 months
  - Technical – e.g., add new model, change in raw materials, etc.
- Approval timelines depend on registration route chosen
  - Standard: 6-8 months, or 2-3 months with TPR
  - Equivalency (US/CA): 6-8 months (cannot use TPR)
  - Equivalency (JP): 2-4 months (cannot use TPR)

**COFEPRIS Fees:** 50-75% of registration cost
Renewals

• Required every 5 years
• Must go through original registration route  
  - TPR review is an option for Standard process renewals only
• Submit to COFEPRIS no later than 150 calendar days before expiration
• Submit Technovigilance Report to national Pharmacovigilance Center (CNFV) at least 90 days before renewal deadline. Report includes:
  - Number of units imported to Mexico per year
  - Any adverse events that occurred during the life of the registration
• Timeline: 6-8 months without TPR, 3-4 months with TPR

COFEPRIS Renewal Fees: US $450-$830
Peru

GDP per capita: $13,300
Health Expenditure: 5.5% of GDP
Median Age: 28 years
Life Expectancy: 74 years
Topics

• Overview of Regulatory Framework
• Regulatory Process
• In-Country Representation
• Post-Approval
Overview of Regulatory Framework and Regulatory Process
DIGEMID, a division of the Peruvian Ministry of Health (MINSA), regulates MDs and IVDs

- Law No. 29459 in force
  - Aspects of the regulatory system are still addressed under prior regulations (D.S. 010-97-SA and Resolution 283-98-SA/DM), and fall under the scope of the Texto Unico de Procedimientos Administrativos-DIGEMID/MINSA al 05 de Marzo 2010. (TUPA)
  - TUPA is published annually and stipulates the requirements that are in force
Classification

- Regulation classifies devices based on risk:
  - Class I (Low risk)
  - Class II (Moderate risk)
  - Class III (High risk)
  - Class IV (Critical risk)
- However, no consistent interpretation
  - DIGEMID may follow manufacturer’s home country classification or the classification of similar devices
Device registration requires information such as:

✓ Free Sales Certificate (CFS)/Certificate to Foreign Government (CFG)
✓ Information re: models and accessories
✓ Packaging
✓ Labeling and IFU (in Spanish)
✓ Testing conducted, and more
### Timeline and Fees

<table>
<thead>
<tr>
<th>Classification</th>
<th>DIGEMID’s Fees</th>
<th>Official Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>S. 1,588 (~$470 USD)</td>
<td>60 days*</td>
</tr>
<tr>
<td>Class II/IIa/IIb</td>
<td>S. 1,872 (~$555 USD)</td>
<td>90 days*</td>
</tr>
</tbody>
</table>
| Class III/IV   | Class III: S. 1,980 (~$585 USD)  
                  Class IV: S. 2,166 (~$640 USD) | 120 days*          |

*Actual timelines are 4-6 months*
In-Country Representation
Peru Registration Holder (PRH)

- Manufacturer must appoint an in-country representative, or PRH
- PRH must be a licensed pharmacy, plus maintain a licensed pharmacist on staff as Technical Director
- PRH will apply for medical device registration and is identified on the labeling
- Distributors obtain their own copy of the registration, in order to import directly
- Only one registration/PRH per product
Post-Approval
Modifications, Vigilance, and Registration Validity

• DIGEMID has “Minor changes” and “Major changes”
• Minor changes are administrative notifications, formal approval isn’t required to market with that change
• Major changes require formal approval
  - Official review time is 60 days; “real-time” ~4-6 months
• Vigilance requirements are issued in RM No. 539-2016
Renewals

- Required every 5 years
- Renewal applications require same information as new registration, e.g., labeling, IFU, CFS
- Modifications cannot be made to the registration during the renewal process
- No deadline to submit renewal application
- DIGEMID fee same as initial registration fee
- Timeline: ~4 months
Questions?
Thank you for your time and attention

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