Diagnostic Regulation in Brazil

AMDM's 2015 IVD Focus Meeting

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ALADDIV – The Latin American Alliance for for the Development of In Vitro Diagnostics

- Non-profit organization, created in 2012, acting in the whole Latin America region, through a network of collaborating members (academy, industries, governments).
- Entity focus on the convergence of interests of the several stakeholders in the IVD segment
- Main activities:
  - Share **knowledge and education in IVD Field**
  - Promote the discussion of the regulatory issues and quality systems with the local Government Agencies, allowing the exchange of experience and discussion in favor of the **convergence or harmonization** of the regulation

INTERNATIONAL WORKSHOPS

"Accessible and Quality Assured *in Vitro* Diagnostic Tests for Public Health Programs"

- Brazil (Brasília), April 2012 (OPAS)
- Brazil (Brasília), November 2012 (ANVISA)
- Brazil (Curitiba), October / November 2013 (TECPAR)
- Brazil (Brasília), November 2014 (ParlaMundi/LBV)
- Peru (Lima), May 2015 (Hotels Meliã)

www.aladdiv.org.br

ANVISA

The National Health Surveillance Agency (ANVISA) was established by Federal **Law 9.782**, of January 26, 1999.

- Protection of Public Health
- Regulation and Control over Health Services, Medical Devices, Drugs, Cosmetics, Sanitizing/Cleaning Products, Food and Tobacco
- Control of Brazilian ports, airports, and borders (customs)
- Coordination of the National Sanitary Surveillance System (SNVS)
- Technical support to the National Institute of Industrial Property on granting patents

Main Regulations for Medical Devices

ALAD DiV

Law N. 6.360/1976

Basis for the regulation of all products under health surveillance in Brazil, including IVD - ANVISA is responsible for medical device registration and to promote the access by the consumers to products that proved to have quality, safety and efficacy.

Resolution RDC 185/2006

Report of Economic Information

- Blood glucose analyzer for outpatient and domestic use (and strips)
- Hepatitis B and C
- HIV
- HTLV
- Syphilis
- Chagas desease
- Neonatal Screening:TSH, T4, Phenylalanine

Main Regulations for Medical Devices

ALADDiV

Resolution RDC 67/2009

Complaint handling

Resolution RDC 23/2011

Field Action

Normative Instruction nº 4/2012

Allows IFU in electronic format for medical devices under certain conditions

Resolution RDC 16⁄2013

QS Regulation for Medical Devices, including IVD

Main Regulations for Medical Devices

Resolution RDC 15/2014

- Establishes requirements to demonstrate compliance with Good Manufacturing Practices (GMP) for marketing authorization of medical devices in Brazil
- GMP Certification as a requirement for marketing authorization of devices class III and IV
- Includes the possibility to use reports from QS audits conducted by third parties (MDSAP report) to obtain ANVISA GMP/QS Certification.

Main Regulations for Medical Devices

ALAD DiV

Law nº13.097/2015

- Authorizes the delegation of inspections to a domestic or international organization duly recognized by ANVISA (MDSAP)
- Market Authorization validity can be extended from 5 to 10 years
  - ✓ Nowadays market authorization is valid for 5 years
  - ✓ Extension under discussion in ANVISA by each Department
  - ✓ Requires specific regulation to be implemented

Normative Instruction ANVISA nº 03/2015

- Establishes criteria for pre-market submissions of products in IVD families

Main Regulations for Medical Devices

ALAD DiV

Interministerial Ordinance 701/2015

- Revision the fees Anvisa to catch up with the inflation accumulated since 1999.
- The fee increase is up to approximately three times and affects any legal entities whose activities are subject to the sanitary surveillance regime (product registration, re-registration, monitoring, domestic and overseas inspection).
- New fees effective since September 9, 2015.

New IVD Regulation - Overview

RDC ANVISA nº 36/2015, Released on: 8/27/2015

- **To be effective:** 10/26/2015
- **Scope**
  - Establishes the products subject to ANVISA regulation as IVD (including instruments), define how to classify such products, submission route (listing or registration) and define the requirements for labeling and instructions for use
- **Products already approved ⇨ legacy products**
  - Risk Class I and II: Brazilian dossier shall be updated to comply with new requirements before 8/26/2016
  - Risk class III and IV: Brazilian dossier shall be updated to comply with new requirements at the re-registration/renewal date

New IVD Regulation - Overview

RDC ANVISA nº 36/2015

Submissions under review and not approved before 10/26/2015

- shall be ammended/updated to comply with new regulation

Re-registration/renewal every 5 years

- Risk Class I and II: no longer required
- Risk Class III and IV: still required

Requirements and documentation aligned with IMDRF IVD Table of Content (ToC)

More rigorous requirements for high risk products (classes III and IV)

Unnanounced inspections: performed by Regulators to verify the compliance (new and legacy products) with new requirements

New IVD Regulation - Overview

Published Aug 27th, 2015	→	Effective Oct 26th, 2015
Approved submissions **"Legacy products"**	→	Update files by Aug 26th 2016
Submissions under review (non-approved)	→	Ammendment to comply with new requirements
Class I, II (listing)	→	No renewal
Class III, IV (registration)	→	Renewal every 5 years
Content based on IMDRF ToC	→	Regulatory Convergence

New IVD Regulation - Overview

RDC ANVISA nº 36/2015 - Legal Documents

1. **Certificate of Foreign Government** or **Certificate of Free Sale**
   - No longer required for risk class I, II, III and IV submission
2. **Authorization Letter**
   - Issued by Legal Manufacturer; Notarized and legalized by Brazilian Embassy
   - Shall state that the Manufacturing site complies with Brazilian GMP/QS Regulation (RDC 16/13) ⇨ very similar to ISO 13485
3. **ANVISA GMP certification / Quality System audit (oversea inspection)**
   - Required for product risk class III and IV

New IVD Regulation - Scope

RDC 36/2015		Comment
In Scope	IVD Class I, II, III, IV IVD Instruments	
Out of Scope	1. Non-built in Software (specific regulation) 2. QC reagents 3. Raw material for *in house* tests 4. *In house* tests 5. Tests for non-human samples 6. General Laboratory Use reagents 7. Forensic tests / doping control tests 8. RUO products 9. Culture media for environmental monitoring	Software is currently grayzone (no specific regulation yet)

New IVD Regulation - Overview

Topics to Review & Understand...

RDC 36/2015	Topic	Is it regulated?
Not applicable to	XI - Software as a Medical Device	Yes. it will be regulated by an specific regulation
Not applicable to	XXIX - Research Use Only product: product with no medical purpose or objective, that can be used in basic research, pharmaceutical research or as component of a reagent kit with research purposes, and that cannot be used for clinical purposes	No. Not considered a regulated product. Cannot be used for clinical purposes

New IVD Regulation - Overview

Topics to Review & Understand...

RDC 36/2015	Topic	Is/will it regulated?
Not applicable to	XXI - **Laboratory Use Only / General Purpose Reagent:** chemical reagent or device for general laboratory use, that is used for preparation and analysis of samples from the human body with diagnostic purposes and that is not labeled or intended for a specific diagnostic application;	Non-regulated
Applicable to	Art 11 – **Risk Class I** a) Reagents or other articles that are auxiliary to in vitro diagnostic procedures b) Products intended for calibration, cleaning or maintenance of instruments during service procedures, or for maintenance or cleaning performed by qualified user, according to indication of the manufacturer specified in the instrument manual	Regulated

Risk class for IVD instrument

INSTRUMENT TYPE	RISK CLASS
Instrument for sample preparation and processing for in vitro diagnostic procedures (example: slide processor)	Class I
Art 12, Sole paragraph. Instruments used for in vitro diagnostic determination using human samples and which generate analytical determinations or results shall always be classified as Class II (flow cytometer)	Class II
Art 10 Products for self-testing shall be classified as Class III products (example: blood glucose monitor)	Class III

Self-testing products
Not allowed for

Products below are **not allowed as self-testing** and cannot be supplied to lay users:

1. Products to verify the presence or exposure to pathogenic organisms or transmissible agents, including agents that cause infectious diseases subject to compulsory notification;
2. Blood typing
3. Genetic testing to determine the presence of or to foresee the susceptibility to a disease or physical condition;
4. Auxiliary in the diagnosis or indication of presence of a disease, tumor or cardiac markers, or condition with serious implications for health;
5. Indication of presence/use of drugs or their metabolites

Note: This prohibition can be changed by ANVISA Board of Directors based on public policies and strategic actions of the Brazilian MOH

Risk Classification

RDC ANVISA nº 36/2015 - Risk Class Classification Rules

Based on the document "Principles of Medical Devices IVD Classification" SG1 Final Document GHTF/SG1/N045:2008

Class	Risk Level	Products
I	Low Individual Risk and Low Public Health Risk	Cleaning solution; maintenance solution (solutions used by Technical Services); lysing solution; cytological dye; culture media (prepared plate); blood collection tubes, IVD instruments, among others
II	Moderate Individual Risk and/or Low Public Health Risk	Monoclonal antibodies; coagulation factors, biochmistry reagents (ex glucose, HDL, LDL); IVD instruments, tests to determine antimicrobial susceptibility,among others
III	High Individual Risk and/or Moderate Public Health Risk	Self testing products; (including instruments) cancer screening, Neisseria meningitidis, among others
IV	High Individual Risk and High Public Health Risk	ABO system ; HIV, HTLV, hepatitis

New IVD Regulation – Tech Dossier

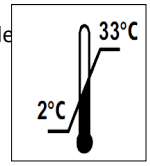
Expected Challenges

Stability Studies

1. **Shelf life:** at least three (3) lots
2. **Product in use:** study to demonstrate product stability after it is opened or installed in an instrument
3. **Transport stability conditions:** required when the transport or shipping are performed under different conditions of storage conditions

Requirements

- Accelerated studies is acceptable BUT real-time studies shall be submitted during the renewal process
- Real-time stability study
- Information: protocol, acceptance criteria, results, conclusion and recommende storage conditions
- Applicable to new products/new submission and Legacy



New IVD Regulation – Tech Dossier

Expected Challenges

Risk Management

- Required for Risk Classes I, II, III and IV
- RM report and the Risk Analysis
  EURA or FMEA (application, design and process)

Manufacturing sites

- Required for Risk Class I, II, III and IV
- Shall be informed all manufacturing sites (for each step), including OEM or 3rd party Company

Global Market History

- Required for Risk Classes I, II, III and IV
- List of countries where the product is authorized or approved to be marketed

New IVD Regulation – Tech Dossier

Expected Challenges

Manufacturing process & Quality Control

- Required for Classes I, II, III and IV
- Flow Chart with a description of each step,
- Includes in process control and finished product tests
- Manufacturing sites names and addresses, including the outsourcing companies

Labeling

- Labels and inserts (IFU) in local Language (Portuguese) and with legend of symbols:
  - For all products for lay users
  - For any product for the symbols that are not cited on ISO 15223

Open item

- Clinical trial x performance characteristics studies (risk class III, IV)

New IVD Regulation – Tech Dossier

Expected Challenges

Peformance Studies

a. Accuracy
b. Precision, including: repeatability, reproducibility
c. Analytical Sensitivity
d. Analytical Specificity
e. Biological samples:
   - characterization and validation of samples (new)
   - storage conditions and samples stability (new)
f. Metrological traceability of calibrators and control material values (new)
g. High dose pro-zone effect (new)
h. Measurement limits or linearity (new)
i. Cut-off value definition (new)
j. Validation of the assay procedure (new)
k. Cleaning and disinfection validation (for instruments that has direct contact with patient or lay user) (new)
l. Usability (human factors) for products for lay users (new)

Technical Dossier
New Requirements

	RDC 36/15 - Listing and Registration Requirements for IVD products (Reagents and Instruments)	Risk Class			
		Listing		Registration	
		I	II	III	IV
Legal documents	**I - Domestic products with any manufacturing step made by a third party** A statement with the legal name and post address of the company(ies) involved, as well as the step(s) in the manufacturing process	x	x	x	x
	II – LETTER OF AUTHORIZATION (LoA), for all imported products Original letter, duly legalized at Brazilian Embassy, issued by the legal manufacturer and no older than two years, authorizing the importer (MAH) to represent and commercialize its product in Brazil, containing at least the following information a) Legal Manufacturer name and complete address b) Name and complete address of the Marketing Authorization Holder (MAH) in Brazil c) Clear authorization to the importer (MAH) to represent and commercialize the product in Brazil; d) Aknowledgement that the Manufacturing site complies with the Brazilian Good Manufacturing Practices for Medical Devices and IVD Medical Devices (QS regulation) according to ANVISA Regulation(RDC ANVISA 16/2013)	x	x	x	x
	III – CERTIFICATE OF GOOD MANUFACTURING PRACTICES ISSUED BY ANVISA GMP / QS certificate issued by ANVISA stating that the manufacturing site complies with Brazilina GMP / QS regulation			x	x

Technical Dossier
New Requirements

	RDC 36/15 - Listing and Registration Requirements for IVD products (Reagents and Instruments)	Risk Class			
		Listing		Registration	
		I	II	III	IV
Technical Dossier - Part 1	**I – PRODUCT INFORMATION, containing the data below:**				
	a) Indication for use or intended use:				
	1. analyte or measurand				
	2. functionality (screening, monitoring, diagnosis or diagnostic support)				
	3. specific situation, condition or risk factor of interest that is intended to detect, define or differentiate				
	4. intended user (professional or lay user)	x	x	x	x
	5. environment or place of use				
	6. whether it will be a single or multiple use				
	7. whether it is automated, semi-automated or not				
	8. whether it is qualitative or quantitative				
	9. the type of specimen/sample (s) required; and				
	10. when applicable, target testing population				

Technical Dossier
New Requirements

	RDC 36/15 - Listing and Registration Requirements for IVD products (Reagents and Instruments)	Risk Class			
		Listing		Registration	
		I	II	III	IV
Technical Dossier - Cont	b) detailed description of the principle of the assay method or instrument principles of operation c) risk class into which the product is classified; d) description of the product components and, where appropriated, description of active ingredients of components; e) description of product configuration and packaging (primary and secondary); f) when applicable, for automatic assays, description of the characteristics of the instrument needed or dedicated; g) when applicable, description of the software to be used with the in vitro diagnostic product; h) when applicable, description or a complete list of all product configurations/variations that will be available i) when applicable, description of the accessories, other in vitro diagnostic products and any other product that shall be used combined with the target product; j) indication of country(ies) where the product is authorized or approved to be marketed.	x	x	x	x
	II- PRODUCT IMAGES photos, drawings or diagrams of the product or the set of components	x	x	x	x
	III – RISK MANAGEMENT REPORT Risk analysis and Risk Control Measurements for reducing the risk [Summary Report + EURA or FMEA (design, process, application)]	x	x	x	x
	IV - LIST OF STANDARDS for design and manufacture, when applicable. At a minimum should include the standard organization, standard number, standard title, year/version.	x List	x List	x List	x List

Technical Dossier
New Requirements

	RDC 36/15 - Listing and Registration Requirements for IVD products (Reagents and Instruments)	Risk Class			
		Listing		Registration	
		I	II	III	IV
Technical Dossier - Cont	**V – PERFORMANCE STUDIES, containing, when applicable:** a) for biological samples: 1. characterization and validation of clinical samples used; and 2. storage conditions and samples stability;		X Report	X Report	X Report
	b) metrological traceability of calibrators and control material values;		X Report	X Report	X Report
	c) measurement accuracy;		X Report	X Report	X Report
	d) measurement precision, including: 1. repeatability; and 2. reproducibility;		X Report	X Report	X Report
	e) analytical sensitivity or limit of detection;		X Report	X Report	X Report
	f) analytical specificity;		X Report	X Report	X Report
	g) high dose pro-zone effect;		X Report	X Report	X Report
	h) measurement range (limits) or linearity;		X Report	X Report	X Report
	i) cut-off value definition		X Report	X Report	X Report
	j) validation of the assay procedure report;		X Report	X Report	X Report
	k) cleaning and disinfection validation report for instruments that require direct contact with the patient or lay user;		X Report	X Report	X Report
	l) usability report for products destined to lay user		X Report	X Report	X Report

Technical Dossier
New Requirements

	RDC 36/15 - Listing and Registration Requirements for IVD products (Reagents and Instruments)	Risk Class			
		Listing		Registration	
		I	II	III	IV
Technical Dossier - Cont	**VI – PRODUCT STABILITY* (real time), except for instruments, containing:** a) shelf life study with a minimum of **3 (three) lots** of the product + recommended storage conditions;* b) in use stability – after product being opened or installed in an instrument;* c) transport or shipping stability + recommended transport conditions, when the transport /shipping are performed in different storage conditions * * it is required: protocol, acceptance criteria, results and conclusion	X Report	X Report	X Report	X Report
	VII – CLINICAL PERFORMANCE, when applicable, including a) general summary of clinical evidences, including clinical sensitivity and specificity b) expected values or reference values; c) clinical evidence evaluation report; d) clinical studies specific for the product			X Report	X Report
	VIII - Label and insert (IFU), containing: a) images of primary and secondary labels to be applied on the products b) instructions for use (IFU) c) for instruments, operator's manual or technical manual.	X	X	X	X
	IX– MANUFACTURING PROCESSES: flowchart describing phases of manufacturing up to the finished product, including IN PROCESS CONTROL and FINISHED PRODUCT TESTING. Identifying ALL the manufacturing sites, where applicable;	X Flowchart	X Flowchart	X Flowchart	X Flowchart
	X– MANUFACTURING SITES: complete addresses , including third parties (contracted by the legal manufacturer) or OEM (Original Equipment Manufacturer);	X	X	X	X

OBRIGADA!!

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