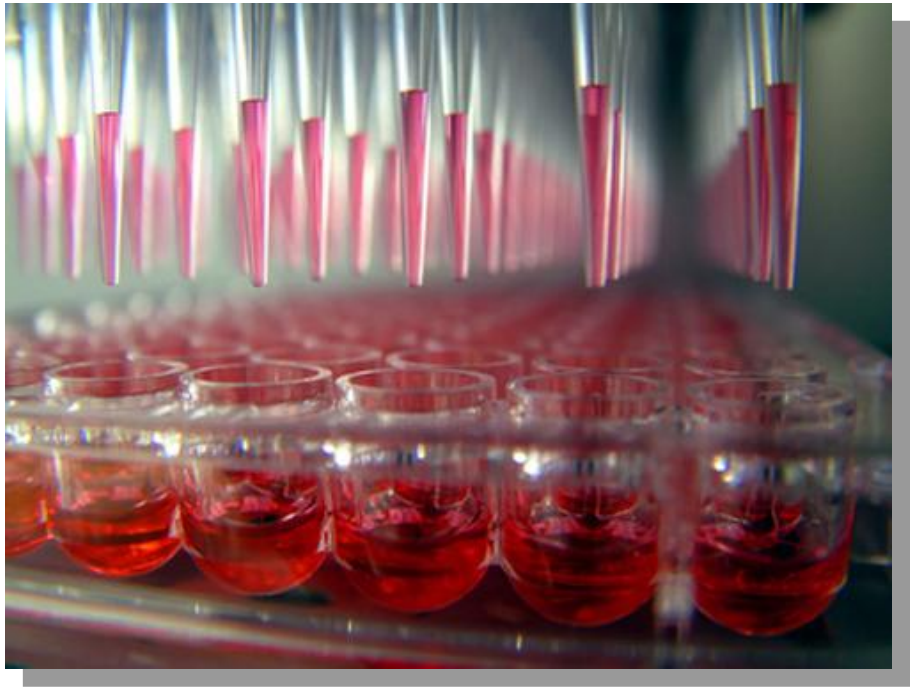
Convergência Regulatória
A experiência brasileira como membro do IMDRF



Augusto Bencke Geyer

Gerência de Produtos para Diagnóstico *in vitro*

ANVISA

Testes Diagnósticos Acessíveis e Qualidade Assegurada para Programas de Saúde Pública

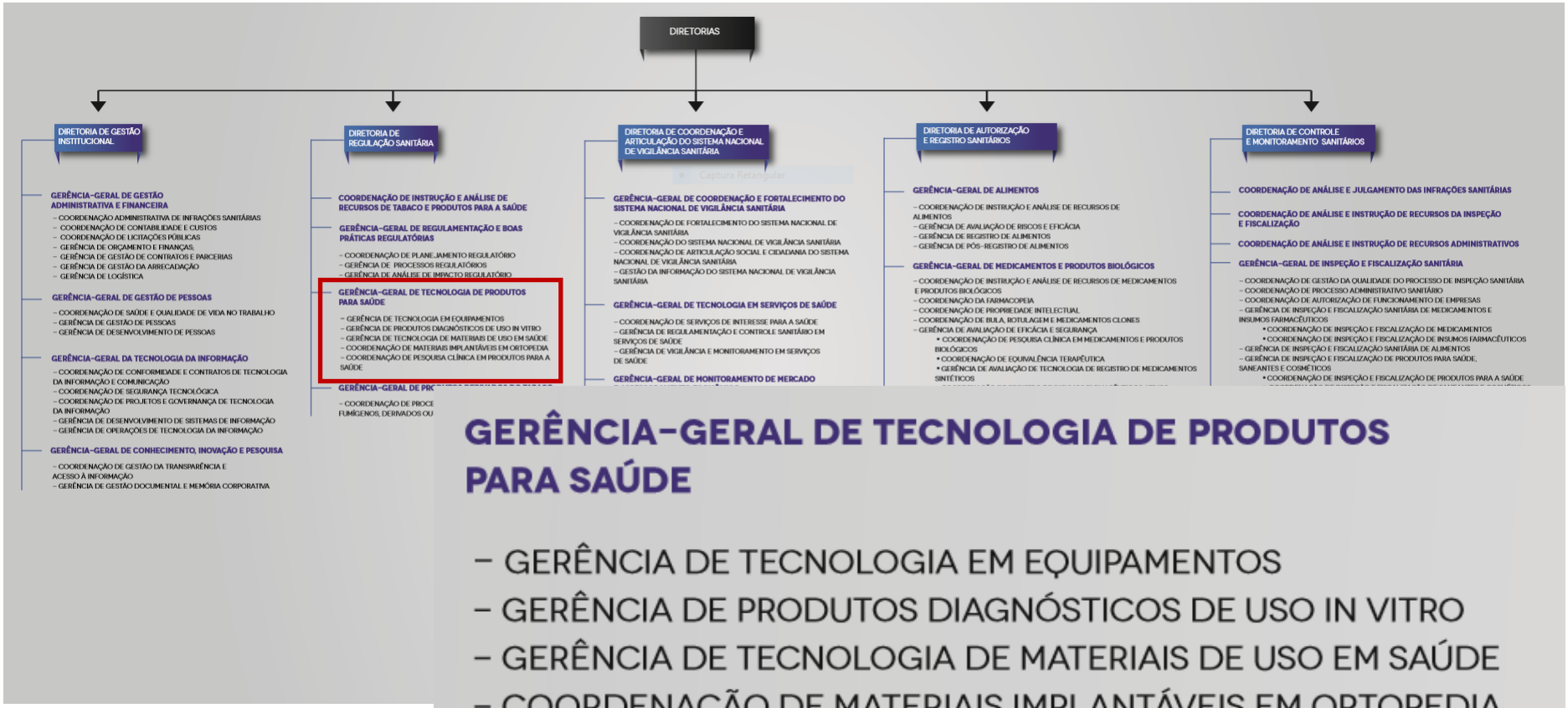
Florianópolis, 15/set/2016

ANVISA – Brazilian Health Regulatory Agency

Integrated with the public healthcare system
Sistema Único de Saúde (SUS)

Established by law in 26 January 1999 – Lei nº 9.782

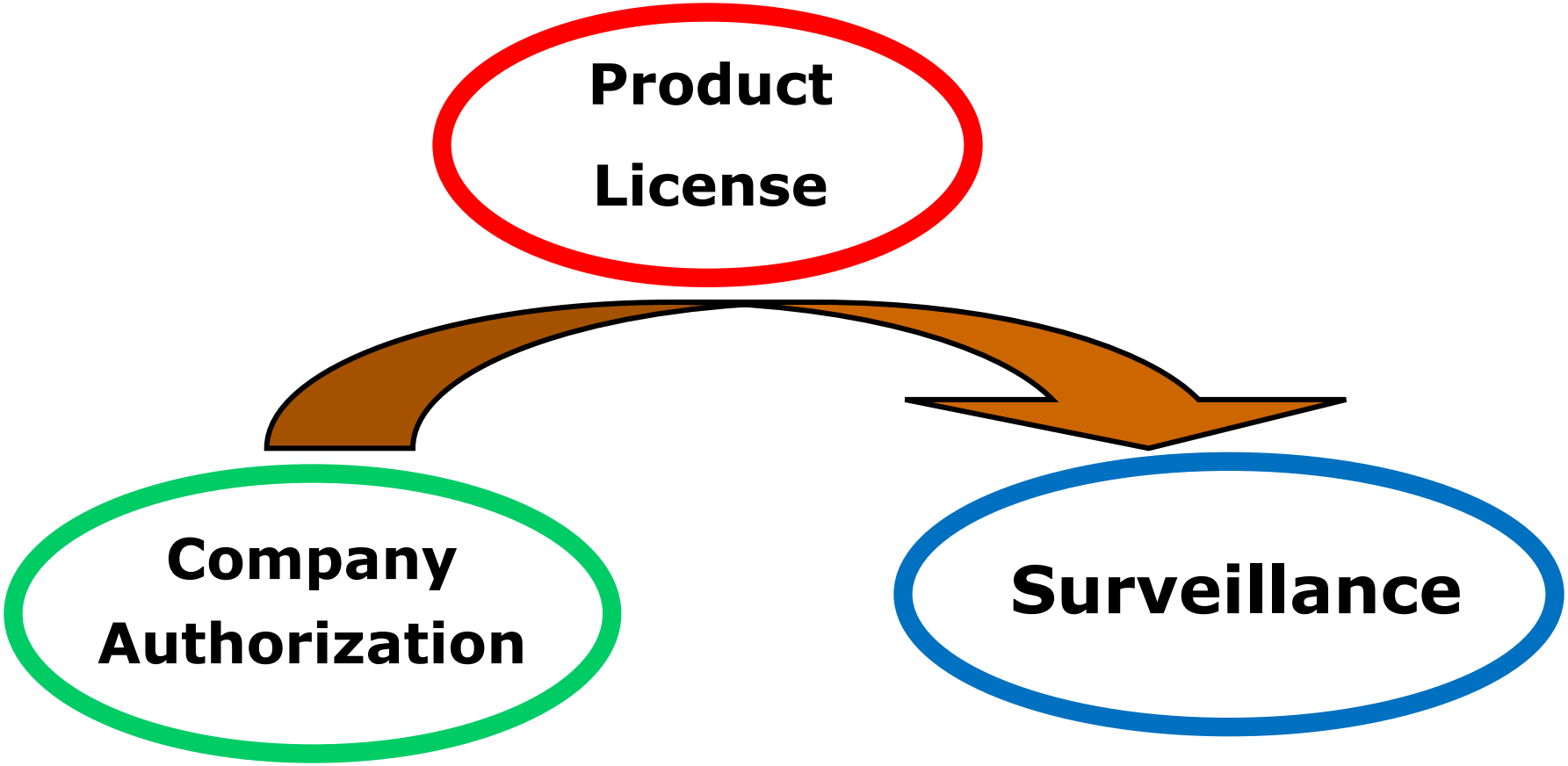
Organization Chart



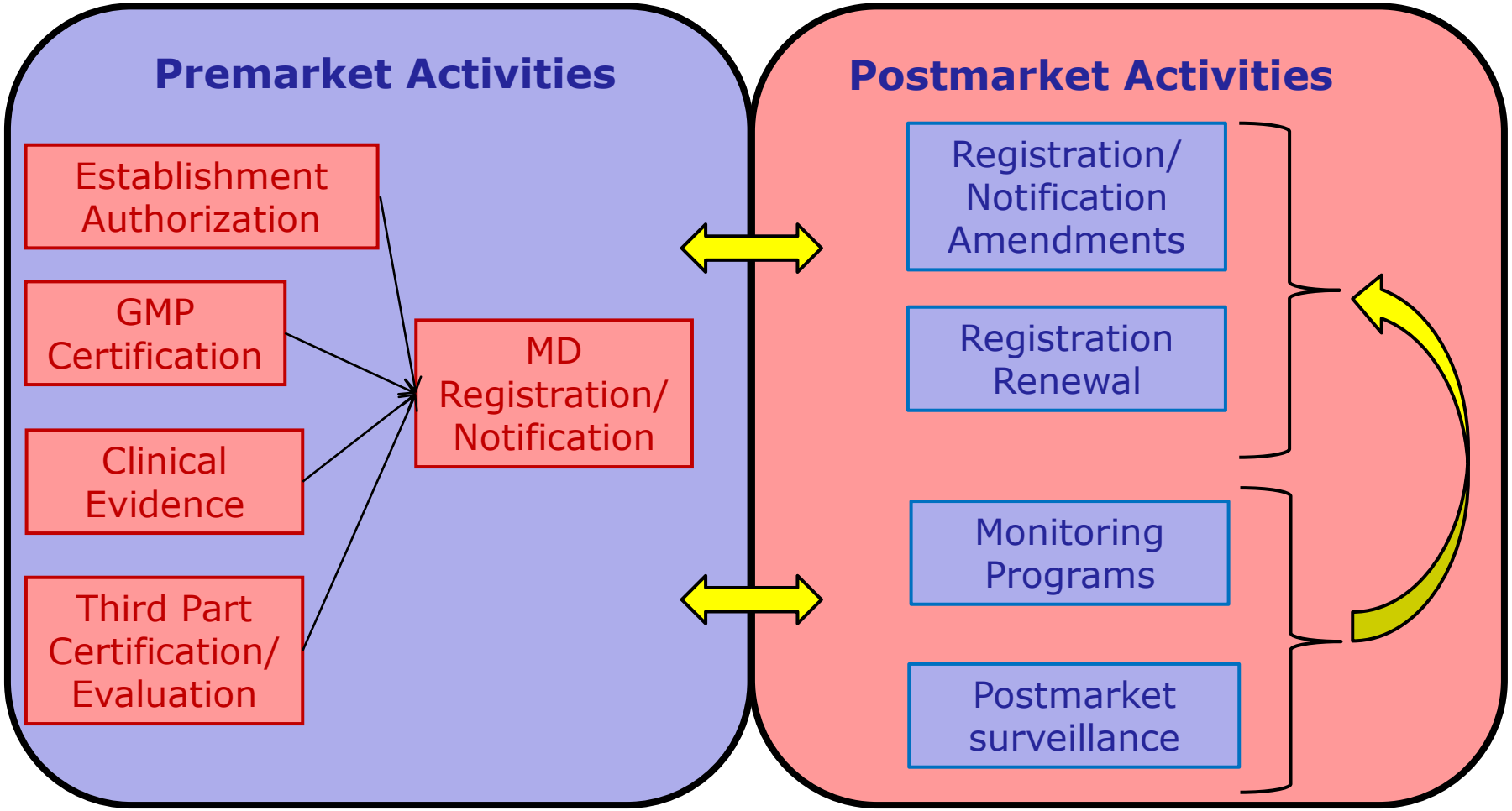
GERÊNCIA-GERAL DE TECNOLOGIA DE PRODUTOS PARA SAÚDE

– GERÊNCIA DE TECNOLOGIA EM EQUIPAMENTOS
– GERÊNCIA DE PRODUTOS DIAGNÓSTICOS DE USO IN VITRO
– GERÊNCIA DE TECNOLOGIA DE MATERIAIS DE USO EM SAÚDE
– COORDENAÇÃO DE MATERIAIS IMPLANTÁVEIS EM ORTOPEDIA
– COORDENAÇÃO DE PESQUISA CLÍNICA EM PRODUTOS PARA A SAÚDE

Sanitary Control of Medical Devices



Overview of the Regulatory Scheme



Main RDCs for MD

- **RDC 185/2001** – Premarket approval process for device and family of devices (non-IVDs)
- **RDC 36/2015** – Premarket approval process for IVDs
- **RDC 56/2001** – Essential Requirements of Safety and Effectiveness
- **RDC 16/2013** – Good Manufacturing Practices Requirements for MD
- **RDC 25/2009** – GMP Certification for MD
- **RDC 40/2015** – MD Notification (non-IVDs)
- There are also other RDCs which defines additional requirements for specifics devices

Products Regulated by the Office of IVDs – GEVIT

- *In Vitro* Diagnostic Medical Devices
  - Reagent kits, calibrators and controls for analytes available on human specimens
    - Proteins
    - Nucleic acids
    - Pathogens
    - Immunoglobulins
    - Metabolites
    - Drugs
    - Other substances
  - Instruments
    - Analyzers
    - Sample preparation

Main Tasks

- Analysis of submissions for registration, notification, renewal, changes and cancellation of IVDs;
- Technical reports to:
  - Departments of Anvisa;
  - Ministry of Health;
  - Public organizations;
  - Users, laboratories and healthcare professionals.
- Answer questions regarding the importation of regulated products to Anvisa inspectors on borders;
- Issuance of IVDs registration requirements;
- Support to Good Manufacturing Practices inspections for certification processes.

Applicable Regulations

- Development of new regulation (2012)
  - Discussions about IVD Table of Contents – 2012-2014
  - Need to update requirements from previous RDC
  - Incorporation of IVD instruments (analyzers)
  - Chance to align with other jurisdictions
  - Chance to know and understand requirements from the IMDRF participants

Applicable Regulations

- RDC ANVISA 36/2015
  - Registration and notification of IVDs
    - Lower risk products (classes I and II) – "Cadastro"
    - Higher risk products (classes III and IV) – "Registro"
  - Risk classification rules
    - Based on GHTF proposal
  - Documental requirements for submission
  - Labeling requirements (including Instructions for Use)
    - Professional or Point of Care User
    - Lay user
  - Technical Dossier
    - Based on the IVD Market Authorization Table of Contents (IMDRF)
  - Good Manufacturing Practices Certification
    - RDC ANVISA 16/2013

Applicable Regulations

- Technical Dossier
  - Product description based on intended use
  - Risk Management
  - Performance Studies
    - Accuracy of measurement
    - Analytical sensitivity
    - Analytical specificity
  - Stability Studies
    - Claimed shelf-life
    - In use stability
    - Shipping stability
  - Clinical Performance
  - Labeling
  - Production flow

IMDRF/RPS WG/N13FINAL:2014

IMDRF International Medical Device Regulators Forum

Final Document

Title: In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)

Authoring Group: Regulated Product Submissions Table of Contents Working Group

Date: 30 June 2014

Jeffrey Shuren, IMDRF Chair

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CH1.08	User Fees
CH1.09	Pre-Submission Correspondence and Previous Regulator Interactions
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Applicable Regulations

CHAPTER 2 – SUBMISSION CONTEXT

Row ID	Heading Class & Level		Heading	Common Content	Regional Content
CH2.1	IMDRF	1	Chapter Table of Contents	a) Includes all headings and sub-headings for the chapter. b) Specifies the page number for each item referred to in the table.	
CH2.2	IMDRF, RF	1	General Summary of Submission	a) Statement of the device type (e.g. Tacrolimus test system, blood specimen collection device, calibrator) and name (e.g. trade name, proprietary name), its general purpose, and a high-level summary of key supporting evidence (i.e. studies that are unique to the risks of this device type). b) Summary of submission, including i. The type of submission (e.g. new, amendment, change of existing application, renewal); ii. if amendment/supplement, the reason of the amendment/supplement; iii. if a change to existing approval, description of the change requested (e.g., changes in design, performance, indications, changes to manufacturing processes, manufacturing facilities, suppliers); iv. any high-level background information or unusual details that the manufacturer wishes to highlight in relation to the device, its history or relation to other approved devices or previous submissions (provides context to submission).	**ANVISA:** If renewal, amendment or change, identification of the registration/notification number issued by ANVISA for the device, family, system or set of devices and the number of the original application must be informed. **EU** If renewal, amendment or change, identification of product (family) currently Marketed under CE mark and related certificate of IVDD annex. **HC** If amendment or new submission based on currently licenced device(s), the Canadian Medical Device Licence Number(s) should be provided along with the description of the change requested. **TGA** If recertification or change to a conformity assessment certificate, identification of the affected TGA certificate numbers must be detailed. **USFDA 510(k)** Executive Summary
CH2.3	Regional (USFDA)	1	Summary and Certifications for Premarket Submissions		**USFDA PMA** a) Summary of the Content of the Whole PMA per 21 CFR 814.20(b)(3) **USFDA 510(k)** a) 510(k) Summary contains all elements per 21 CFR 807.92 **OR** b) 510(k) Statement contains all elements per 21 CFR 807.93
CH2.4	IMDRF	1	Device Description	**NO CONTENT AT THIS LEVEL**	
CH2.4.1	IMDRF, RF	2	Comprehensive Device Description and Principle of Operation	a) A general description of the device, including: i. A statement of the device name. ii. What does it detect? iii. Who uses it and for what? (high level statement) iv. Where to use it? (places/environment where the device is intended to be used) v. General description of the principle of the assay method or instrument principles of operation. vi. Description of the components (e.g. reagents, assay controls and calibrators) and where appropriate, a description of the reactive ingredients of relevant components (such as antibodies, antigens, nucleic acid primers). vii. If applicable, labelled pictorial representation (diagrams, photos, drawings). viii. If system, how the components relate? ix. If applicable, identify if the device incorporates software/firmware and its role. b) Product specification, including: i. Physical characteristics of relevance to the end user (dimensions, weight) ii. If applicable, technical features and operating modes	**ANVISA:** a) Some accessories may request independent submission at ANVISA. Especially when it is considered a medical device by itself and is not of exclusive use of the medical device to be used in combination. For this accessories shall be identified and heir registration/notification number in ANVISA provided. **HC and USFDA** Components or accessories that can be sold separately should be identified. **JP:** Explain that the established product specifications are necessary and sufficient to ensure the efficacy, safety, and quality of the product. **USFDA PMA:** Color Additive information per item A 6.a.ii in Appendix A of the ***Acceptance and Filing Reviews for Premarket Approval Applications (PMAs): Guidance for Industry and Food and Drug Administration Staff Guidance***; 21CFR 814.20(f)

Applicable Regulations

CHAPTER 3 – ANALYTICAL PERFORMANCE AND OTHER EVIDENCE

Row ID	Heading Class & Level		Heading	Common Content	Regional Content
CH3.1	IMDRF	1	Chapter Table of Contents	a) Includes major headings for the chapter, to the level of the custom headings. b) Specifies the page number for each item referred to in the table.	
CH3.2	IMDRF	1	Risk Management	a) A summary of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. The summary should address i. Possible hazards for the IVD medical device for example, the risk from false positive or false negative results and the risk of delays in availability of results ii. Indirect risks which may result from IVD medical device-associated hazards, for example, risk associated with instability, which could lead to erroneous results **or** user-related hazards, such as reagents containing infectious agents. b) The results of the risk analysis should provide a conclusion with evidence that remaining risks are acceptable when compared to the benefits. c) Where a standard is followed, identify the standard.	**EU** A formal signed statement accepting the residual risk upon completing the risk-benefit analysis before placing product on the EU market.
CH3.3	IMDRF (ANVISA, EU, JP, TGA)	1	Essential Principles (EP) Checklist	a) An EP checklist established for the IVD medical devices, information about method(s) used to demonstrate conformity with each EP that applies, references for the method adopted and identification of the controlled document with evidence of conformity with each method used. b) For the controlled documents indicated which are required for inclusion in the submission: a cross-reference of the location of such evidence within the submission. c) If any EP indicated in the checklist does not apply to the device: a documented rationale of the non-application of each EP that does not apply. **NOTE:** Methods used to demonstrate conformity may include one or more of the following: a) conformity with recognised or other standards; b) conformity with a commonly accepted industry test method(s); c) conformity with an in-house test method(s); d) the evaluation of pre-clinical and clinical evidence; e) comparison to a similar device already available on the market.	
CH3.4	IMDRF (ANVISA, EU, HC, TGA, USFDA)	1	Standards	**NO CONTENT AT THIS LEVEL**	
CH3.4.1	IMDRF, RF (ANVISA, EU, HC, TGA, USFDA)	2	List of Standards	a) List the standards that have been complied with in full or in part in the design and manufacture of the device. b) At a minimum should include the standard organization, standard number, standard title, year/version, and if full or partial compliance. c) If partial compliance, a list the sections of standard that i. Are not applicable to the device, and/or ii. have been adapted, and/or iii. were deviated from for other reasons – discussion to accompany	**EU NOTE** An overview of used standards typically is added in the essential requirements checklist, including rationales for using standards that are non-harmonised or complied with only in part. This information needs only to be presented once in the application. **TGA** This list should include any medical device standard or conformity assessment standard that has been applied to the device; and, if no medical device standard or conformity assessment standard, or part only of such a standard, has been applied to the device — the solutions adopted to ensure that each device complies with the applicable provisions of the essential principles. The information in this section may be presented in the Essential Principle Checklist and, if so, needs only to be presented once in the application. **USFDA PMA and 510(k)**

Applicable Regulations

- Laboratory Evaluation ("Análise Prévia")
  - *Instituto Nacional de Controle de Qualidade em Saúde*
  - Kits tested against commercial serological panels and qualified panels developed by the laboratory reflecting the epidemiologic reality in Brazil, including seroconversion samples
  - IVDs submissions that requires "Análise Prévia":
    - Chagas disease
    - HBV
    - HCV
    - HIV
    - HTLV
    - Syphilis
    - Immunohematology reagents
    - Dengue

INCQS
Instituto Nacional de Controle de Qualidade em Saúde

Applicable Regulations

Four Classes according to **RDC 36/2015**:

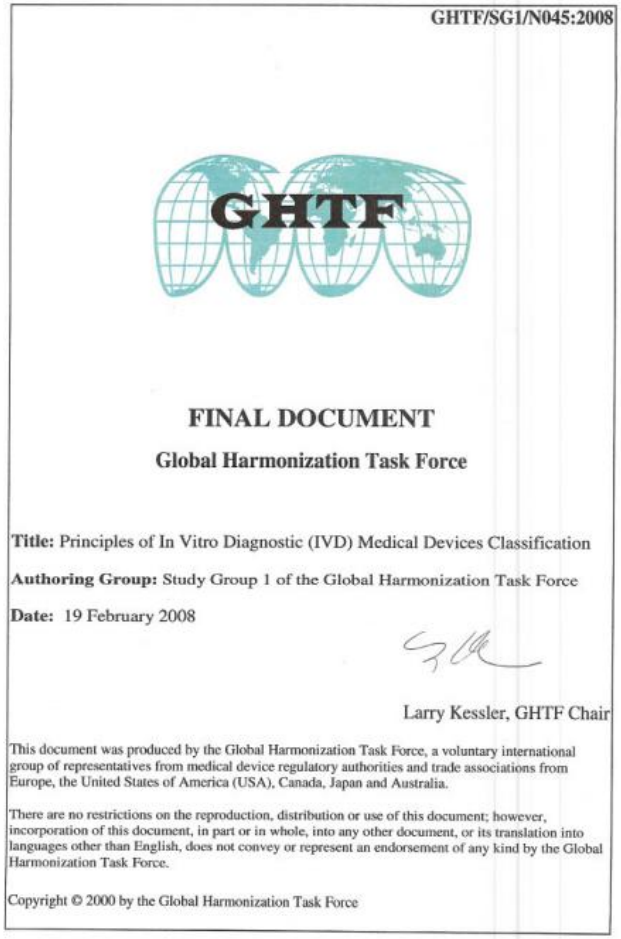
Class I - low risk devices to the individual and low risk to public health

Class II - medium risk devices to the individual and/or low risk to public health

Class III - high risk devices to the individual and/or medium risk to public health

Class IV - high-risk devices to the individual and high risk to public health

9 Rules are used to classify the IVDs according to their intended use, based on GHTF Principles of In Vitro Diagnostic (IVD) Medical Devices Classification



GHTF/SG1/N045:2008

GHTF

FINAL DOCUMENT

Global Harmonization Task Force

Title: Principles of In Vitro Diagnostic (IVD) Medical Devices Classification

Authoring Group: Study Group 1 of the Global Harmonization Task Force

Date: 19 February 2008

Larry Kessler, GHTF Chair

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Applicable Regulations

Risk Class	% Valid Licenses
I	26%
II	52%
III	19%
IV	3%

244 companies (manufacturers and importers)

~ 11600 valid licenses (active)

82% imported products

Applicable Regulations

- RDC ANVISA 36/2015
  - Registration (classes III and IV)
    - Valid for 5 years
    - Must be renewed
    - Full technical dossier must be submitted
    - GMP certification is required
  - Notification (classes I and II)
    - No renewal
    - Simplified technical dossier
    - GMP must be followed

Applicable Regulations

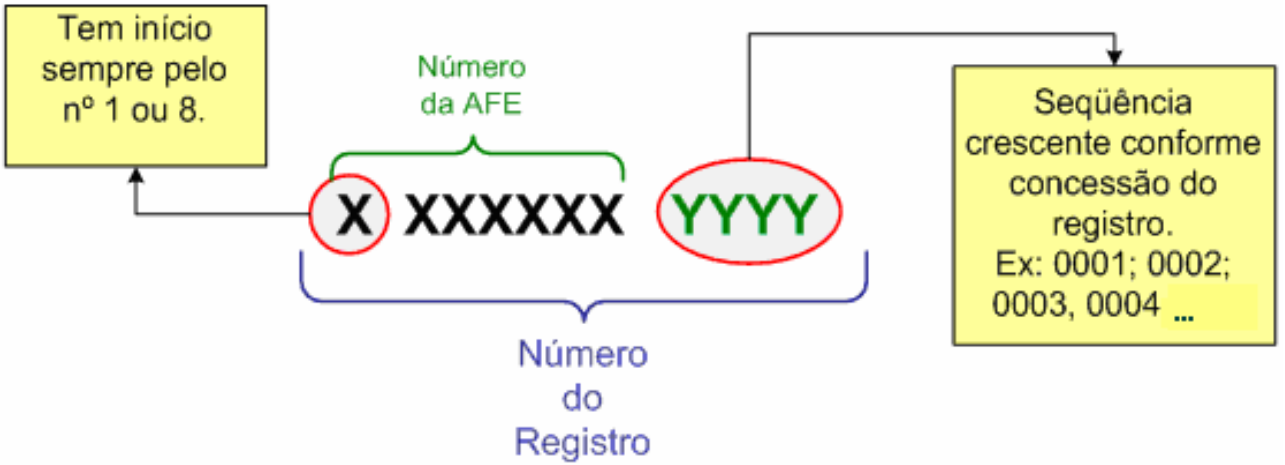
- RDC ANVISA 36/2015
  - All labeling must be in Portuguese
  - For imported devices it is allowed the importation without labels in Portuguese. However, all labels and companion documents must be translated into Portuguese before distribution
  - E-labeling is allowed according to requirements of IN 04/2012, except for some types of devices (e.g. the ones indicated for home use and/or operation by lay user).

Applicable Regulations

- RDC ANVISA 36/2015
  - Points aligned to other regulations
    - Documental requirements
      - Letter (declaration) from the manufacturer authorizing Brazilian representative company
      - No need for Free-Sale-Certificate
      - Adoption of the IMDRF Table of Contents
      - Regulatory convergence
    - Lower risk products – simplified process
    - Higher risk products – strengthened process
    - Specific labeling requirements for lay-user products
    - Rules for product grouping
    - Manufacturer and/or importer responsibility

Applicable Regulations

- Registration/Notification number
  - Must be available on labels
  - Identify license of the product



Applicable Regulations

- RDC ANVISA 52/2015
  - Rules for the registration of HIV self-testing
    - RDC 36/2015 does not allow registration of self-testing IVDs for infectious diseases, tumor and cardiac markers, genetic disorders, blood typing and drugs
    - Exception for public policies developed by the Ministry of Health
  - Regulates the commerce of HIV self-testing IVDs in pharmacies, drugstores and health services to increase access to diagnosis and treatment and help the infection control
  - Additional requirements in terms of labeling

Applicable Regulations

- RDC ANVISA 52/2015

Advantages	Concerns
Acceptability	Extended window period
Expanded access	False negative results during acute phase of infection
Possibility to repeat test	False positive results and consequences
Confidentiality and privacy	Monitoring
Mutual testing	Appropriate use of the product
De-stigmatisation of the disease	Clear understanding of the results obtained

Applicable Regulations

- RDC ANVISA 52/2015
  - Rules for the registration of HIV self-testing
    - Additional labeling requirements
      - Pre and post-test information to the user
      - Warnings, precautions, limitations, window period
      - Negative results does not eliminate possibility of infection
      - Interpretation of results and confirmation
      - Accessible language to any user
      - User aware of risks when using the product
    - Availability of communication channel (telephone) 24/7

Regulated Product Submission

- Benefits of RPS
  - Multiple regions using a harmonized, consistent format
    - Reducing IT burden in industry
  - Minimal revisions needed to address regional differences and/or requirements in content
  - End result is an IT format that can be reused for multiple regions, saving time and resources by mitigating the risk of significantly different methods being developed amongst regulators

- RPS implementation will take several years
- Investment and adjustments on IT tools needed

Table of Contents Pilot Plan

- Pilot Objectives
  - To develop and validate documentation supporting the use of the IMDRF ToCs using feedback from industry participants
  - To identify potential challenges in the industry process and develop proposals on how these can be addressed
  - To provide industry and regulators with experience using the ToCs with real submissions in a controlled setting
  - To evaluate the proper usage of the ToC headings including the appropriate placement of documents within the headings and submission of complete and relevant content
  - To identify additional ToC harmonization opportunities
  - To establish and ensure ToC pilot technical guidelines

Table of Contents Pilot Plan

- Australia, Brazil, Canada, China, EU and the United States are participating regions
- Regional pilots are also currently being undertaken by some IMDRF members
- Pilot initiated October 1, 2015
- 22 requests received, 11 accepted – 10 nIVD, 1 IVD
- Teleconferences to discuss impressions
  - Only a few applications received to date – Extension (?)
- Pilot ongoing with but some manufacturers delaying submitting
- Differences in interpretation amongst regions
- Small sample size, need more applicants to ensure implementation is successful
- To be finalized in September 2016 (?)

Post-Market Activities

- Glucosemeters
  - Usability evaluation of instructions for use
  - Adjustments to the instructions for use suggested to the importers/manufacturers
  - Next step – performance evaluation of the products available on Brazilian market
  - To include in the list of IVDs subject to laboratory challenge ("análise prévia")

- Dengue IVDs
  - Preparation of a qualified serological Dengue panel (subtypes 1, 2, 3 and 4)
  - Laboratory evaluation of Dengue IVDs
  - Reports submitted to the manufacturers/importers
  - Action plans


NOTIVISA
Sistema de Notificações em Vigilância Sanitária
Acesso ao Sistema
apresentação manual cadastro esquemas XML alertas legislação relatórios links de interesse fale conosco
Alertas de 2016
Alertas de 2015
Alertas de 2014
Alertas de 2013 (a partir de 13 de novembro)
Alerta 1324: Alerta de segurança sobre o SISTEMA DE RESSUSCITAÇÃO AUTOPULSE MOD. 100, da Zoll
Alerta 1323: Alerta de segurança sobre ACELERADOR LINEAR ELEKTA, da Elekta
Alerta 1322: Alerta de segurança para uso da máquina HOMECHOICE PARA DIÁLISE PERITONEAL, da Baxter
Alerta 1321: Possibilidade de fratura do fio do sistema de liberação do dispositivo ENDOPRÓTESE ANACONDA, da Terumo
Alerta 1320: Alerta sobre os Produtos ADVIA 1200 Chemistry System – Registro nº 10345160456; ADVIA 1650 Chemistry System - Registro nº 10345160453; ADVIA 1800 CHEMISTRY SYSTEM - Registro nº 10345160636; ADVIA 2400 Chemistry System - Registro nº 10345160471
Alerta 1319: Alerta sobre o Produto Agulha Descartável EMBRAMAC – Registro 10201230119
Alerta 1318: Alerta sobre o Produto Agulha Descartável EMBRAMAC – Registro 10201230081
Alerta 1317: Alerta sobre o Produto Dissector PKS Lyons (Classe de Risco II - Médio Risco), registrado pela empresa Flex Lab
Mais destaques
Observação: Alguns formularios ainda não estão disponiveis pelas vias comuns de acesso ao sistema
Formulário de biovigilância
Acesse aqui
Formulário para notificar reação à doação de sangue
Acesse aqui
Cidadão/ Paciente/ Familiar
Notifique aqui
Profissional de saúde/ Instituição de saúde
Notifique aqui
sistema
Requisitos
Dificuldade no acesso
Agência Nacional de Vigilância Sanitária

Zika IVDs

- Increased number of reported cases of microcephaly in the northeast of Brazil

- ANVISA's Director of Authorizations and Registrations decided on mid January:
  - To prioritize (fast-track) the analysis of submissions for Dengue, Chikungunya and Zika IVDs

- Concerns raised during the review of dossiers:
  - Low number of paired positive confirmed samples
  - Cross-reactivity with Dengue virus and other flavivirus

Zika IVDs – Perspectives

- Intention to extend the collaboration with *Instituto Nacional de Controle de Qualidade em Saúde*
  - Inclusion of Dengue and Zika virus to the "Análise Prévia" scheme (Laboratory Evaluation)
  - Obtain and validate positive samples for Zika virus
  - Reference materials

INCQS
Instituto Nacional de Controle de Qualidade em Saúde

- Adopt WHO recommendations for review of future submissions

World Health Organization

Agência Nacional
de Vigilância Sanitária

MANUAL PARA REGULARIZAÇÃO DE PRODUTOS PARA DIAGNÓSTICO *IN VITRO* NA ANVISA

Gerência de Produtos para Diagnóstico *in vitro* – GEVIT

BRASÍLIA, JUNHO DE 2016

- Guide to the companies which intend to submit dossiers for product licensing
- Available on-line
- Frequently updated

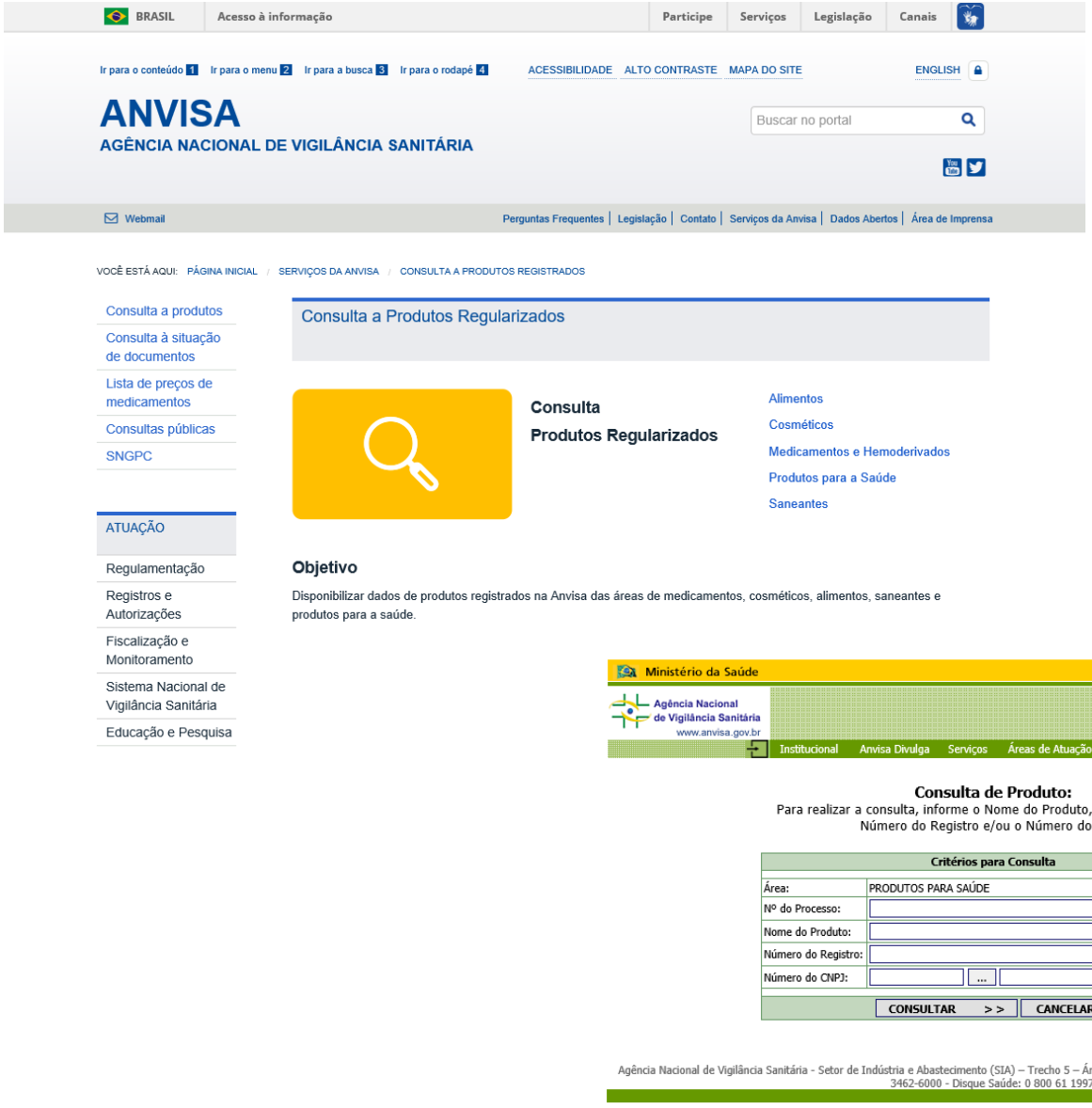
DIAGNÓSTICO IN VITRO :

REGISTRO/CADASTRO CLASSES I, II E III

Exportar para Excel | Voltar | Pesquisar

Ordem numérica	Data de entrada	Expediente	Processo	Código de Assunto	Descrição do Assunto
1	30/03/2016	1441540162	25351967315201657	8437	IVD - Cadastro de produtos importados em família
2	30/03/2016	1444030160	25351968839201647	8436	IVD - Cadastro de produto importado
3	30/03/2016	1444094166	25351968872201621	8002	IVD - Registro de produto importado
4	30/03/2016	1444123163	25351968892201664	8436	IVD - Cadastro de produto importado
5	30/03/2016	1444225166	25351968960201665	8002	IVD - Registro de produto importado
6	30/03/2016	1450774169	25351970020201605	8436	IVD - Cadastro de produto importado
7	30/03/2016	1450787161	25351970032201679	8436	IVD - Cadastro de produto importado
8	30/03/2016	1450795161	25351970037201619	8436	IVD - Cadastro de produto importado
9	30/03/2016	1450903162	25351970121201632	8436	IVD - Cadastro de produto importado
10	31/03/2016	1451037165	25351970213201683	8436	IVD - Cadastro de produto importado
11	31/03/2016	1451075168	25351970245201697	8436	IVD - Cadastro de produto importado
12	31/03/2016	1451289161	25351970378201634	8436	IVD - Cadastro de produto importado
13	31/03/2016	1459585161	25351974215201631	8437	IVD - Cadastro de produtos importados em família
14	01/04/2016	1457500161	25351972959201681	8017	IVD - Registro de produtos importados em família
15	01/04/2016	1458710166	25351973634201686	8434	IVD - Cadastro de produto nacional
16	01/04/2016	1691674163	25351046198201648	8017	IVD - Registro de produtos importados em família
17	04/04/2016	1494024168	25351979975201616	8436	IVD - Cadastro de produto importado
18	04/04/2016	1514185163	25351980051201673	8436	IVD - Cadastro de produto importado
19	04/04/2016	1514201169	25351980062201614	8436	IVD - Cadastro de produto importado
20	05/04/2016	1490313160	25351978589201609	8437	IVD - Cadastro de produtos importados em família
21	05/04/2016	1515803169	25351981140201634	8436	IVD - Cadastro de produto importado
22	07/04/2016	1524746165	25351985766201699	8003	IVD - Registro de produto nacional
23	07/04/2016	1537538162	25351988952201681	8436	IVD - Cadastro de produto importado

- List of submissions waiting for review
- Available on-line
- Daily updated
- Transparency



- Search for licensed medical devices
  - By name
  - By license number
  - By applicant (company)

Gerência de Produtos para Diagnóstico *in vitro*

André Sinoti (E)
Augusto Geyer (E)
Carolina Gasparin (T)
Christiane Coelho (E)
Deborah Araújo (A)
Luciana Averbeck (E)
Marcella Abreu (E)
Marisa Adati (C)
Sheila Sampaio (A)
Valter Pereira (E)

Thank you
Gracias
Obrigado

Office of *In Vitro* Diagnostics

+55 61 3462 6635

augusto.geyer@anvisa.gov.br