Bio-Manguinhos

Experience – CTD Format

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Ministério da Saúde

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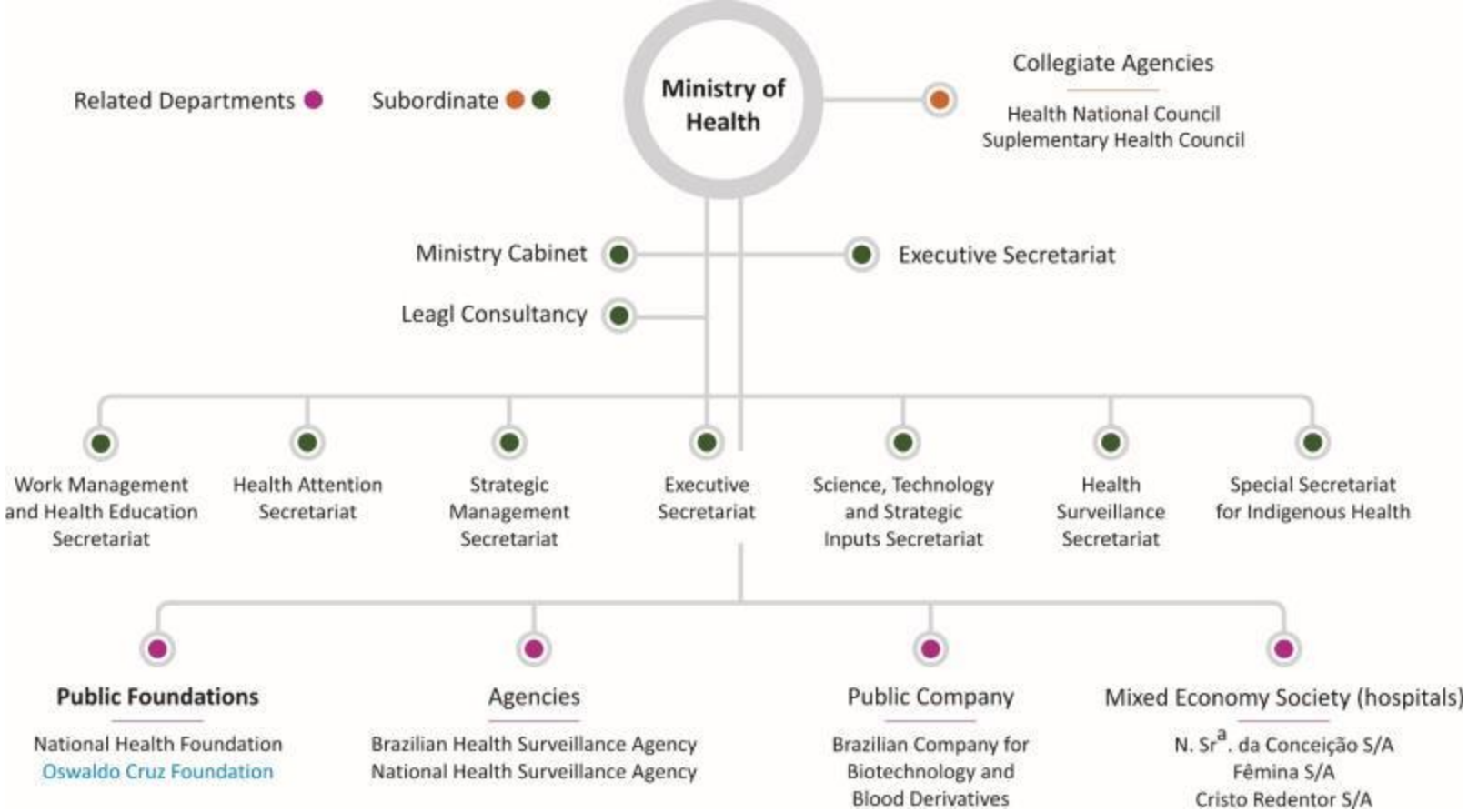
Bio-Manguinhos

Bio-Manguinhos _ Brief Introduction

Ministry of Health _ Organizational Chart



Bio-Manguinhos _ Brief Introduction

Mission

Contribute to the improvement of the standards of the Brazilian public health through innovation, technology development, production of immunobiologicals and services to meet firstly to the demands of the country's health.

Bio-Manguinhos _ Brief Introduction

Portifolio

IVD Reagents

12

Vaccines
10

Biopharmaceuticals

5

- DTP+Hib
- Yellow Fever (Prequalified - WHO)
- Hib
- Meningococcal AC
- Pneumococcal 10-valent, conjugated
- Polio 1, 3 Oral
- Inactivated Poliomyelitis
- Human rotavirus
- Measles, Mumps and Rubella
- Measles, Mumps, Rubella and Varicella vaccine

ANVISA_ Current Requirements _Biologicals Registration

Resolution – RDC n°55/2010

Provides on the registration of new biological products and biological products.

Applicable to:

I. Vaccines
II. Antivenom immunoglobulins
III. Blood products
IV. Biomedicines, obtained from: Biological fluids or animal tissues , Biotechnological procedures
V. Monoclonal antibodies
VI. Medicines containing live, attenuated or dead microorganisms
VII. Probiotics
VIII. Allergens

ANVISA_ Current Requirements _Biologicals Registration

RESOLUTION – RDC n°55/2010

Legal

- Registration application forms - FP1 & FP2,
- Company's Business License
- Technical Responsibility Certificate
- GMPc issued by Anvisa
- Proof of registration of the country of origin

Quality & Production

- Production flowchart
- Quality Control
- Stabilities Studies
- Description of the master and working seed batches of the virus and cell lineage
- Cold Chain Validation

Safety and Efficacy

- Nonclinical studies
- Complete protocols and reports of the clinical studies, phases I, II and III
- Pharmacovigilance and a risk minimization plan

ANVISA_ Current Requirements _Biologicals Registration

Resolução da Diretoria Colegiada – RDC n°55/2010

- Anvisa accept the dossier submission according to CTD format
- Portuguese Language (exception for clinical information)
- It is not mandatory send samples to National Quality Control Laboratory during the registration process
- The structure of the documentation is stablished by the checklist available in the website

ANVISA_ Current Requirements _Biologicals Registration

Resolução da Diretoria Colegiada – RDC n°55/2010

Agência Nacional de Vigilância Sanitária
www.anvisa.gov.br

Consulta de Assuntos

Documentos de Instrução
Área: Medicamento
Assunto: 1528 - PRODUTO BIOLÓGICO - Registro de Produto Novo

Relação de Documentos de Instrução
1 - Formulários de petição de registro - FP1 e FP2 devidamente preenchidos
2 - Via original do comprovante de pagamento da Taxa de Fiscalização de Vigilância Sanitária (GRU)
3 - Cópia de Licença de funcionamento da empresa ou alvará sanitário atualizado
4 - Cópia do Certificado de Autorização de Funcionamento da Empresa ou de sua publicação em D.O.U
5 - Cópia do Certificado de Responsabilidade Técnica - CRT
6 - Justificativa técnica para o registro do produto
7 - Cópia do CBPF, expedido pela ANVISA para todos os fabricantes do princípio ativo, do produto biológico a granel, do produto biológico em sua embalagem primária, do produto biológico terminado, do diluente e do adjuvante.
8 - Cópia do CBPF, emitido pela autoridade sanitária competente do país onde se localiza o fabricante do princípio ativo, do produto biológico a granel, do produto biológico em sua embalagem primária, do produto biológico terminado, do diluente e do adjuvante
9 - Histórico da situação de registro em outros países, quando for o caso
10 - Cópia do comprovante do registro do país de origem do produto biológico, emitido pela respectiva Autoridade Sanitária competente
11 - Bulas do país de origem aprovadas pelas autoridades do país de origem e sua tradução juramentada
12 - Modelos de bula e embalagens primária e secundária, de acordo com a legislação vigente
13 - Código de barra (GTIN) para todas as apresentações ou mecanismos de identificação e segurança de acordo com a legislação vigente
14 - Cópia do compêndio nacional, internacional ou interno da empresa com a determinação das especificações do produto biológico terminado
15 - Informações adicionais de acordo com a legislação vigente sobre o controle de EET, quando aplicável
16 - Relatório Técnico do Produto
17 - Relatório de Experimentação Terapêutica
18 - Relatório de farmacovigilância
19 - Relatório do estudo de imunogenicidade
20 - Plano de farmacovigilância e plano de minimização de risco
21 - 1(um) CD-ROM com a mesma informação documentada gravada em linguagem eletrônica tipo pdf
22 - Documento indicando nome e endereço de todos os fabricantes envolvidos na produção do princípio ativo, do produto biológico a granel, do produto biológico em sua embalagem primária; do produto biológico terminado, do diluente, do adjuvante e do local de liberação do lote
23 - Documentação de Produção e Controle de Qualidade, conforme seções III, IV, V da RDC 55/2010.

Legal

Technical

Clinical

ANVISA_International Council of Harmonization ICH

- ❑ Anvisa accept as member in ICH assembly - November 2016
- ❑ Five years to implement five guidelines

E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B – Clinical Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2D – Post Approval Safety Data Management: Definitions and Standards for Expedited Reporting

M4 – The Common Technical Document (CTD)

M1 – Medical Dictionary for Regulatory Activities (MedDRA)

ANVISA_International Council of Harmonization ICH

- ❑ Anvisa published a draft Guideline for CTD

- ✓ The document do not intend indicate the necessary and technical studies ⟶ Organization

- ✓ Harmonization of terms - Ex: Active Substance ⟶ Active Pharmaceutical Ingredient

- ✓ Facilitate the communication between Manufacturers and the ANVISA

- ✓ Reduce significantly the time to prepare the process registration

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ANVISA_International Council of Harmonization ICH

DCVMN Working Group

- ❑ DCVMN commissioned a comparative analysis of CTD requirements in different countries

- ❑ DCVMN provide the database with the requirement adopted and the participants reviewed the outcome, made corrections and adjustment.

- ❑ Regulatory Affairs Experts from different Manufactures (DCVMN and IFPMAS) worked in groups in order to analyze:

- ✓ Module 1 – 10 countries
- ✓ Modules 2 to 5 – 2 regions and 3 countries
- ✓ Application form – 8 countries
- ✓ Registration procedures of 134 importing countries

The analysis indicates a high degree of divergence.

Manufactures from:

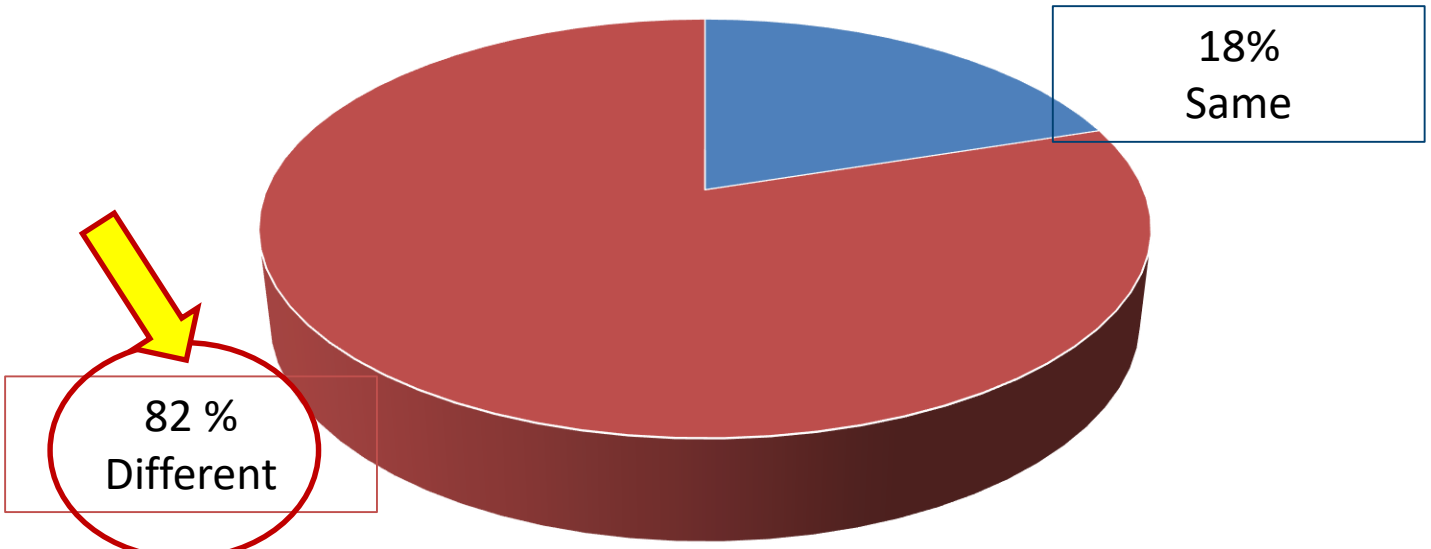
Indian, Indonesian, China, Korea, USA, Europe, Brazil

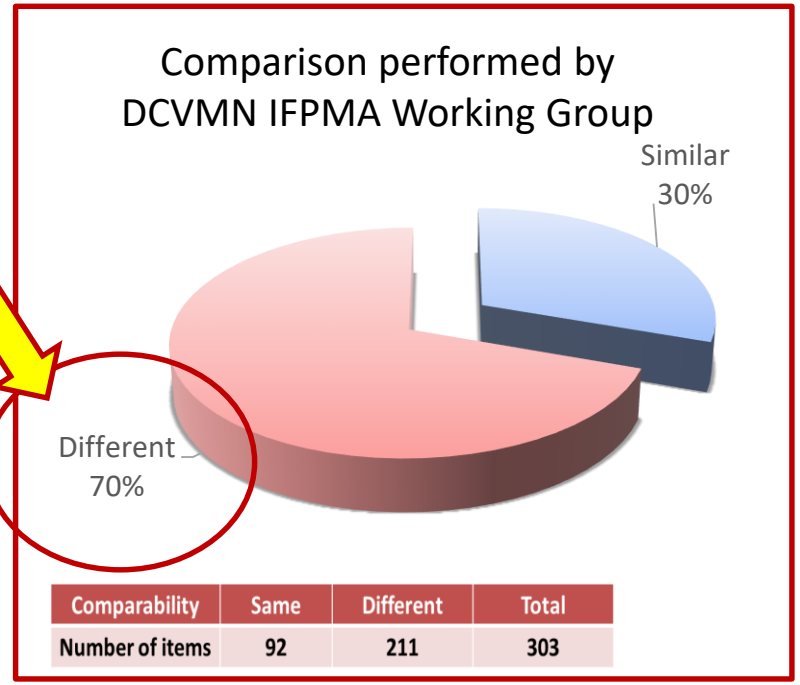
ANVISA_International Council of Harmonization ICH

Anvisa Draft Guideline and ICH CTD Format

- Methodology from DCVMN-IFPMA working group

COMPARISON OF CTD MODULE 1 NUMBERING FROM EUROPE - ANVISA DRAFT GUIDELINE





Comparability	Same	Different	Total
Number of items	92	211	303

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ANVISA_International Council of Harmonization ICH

Anvisa Draft Guideline and ICH CTD Format

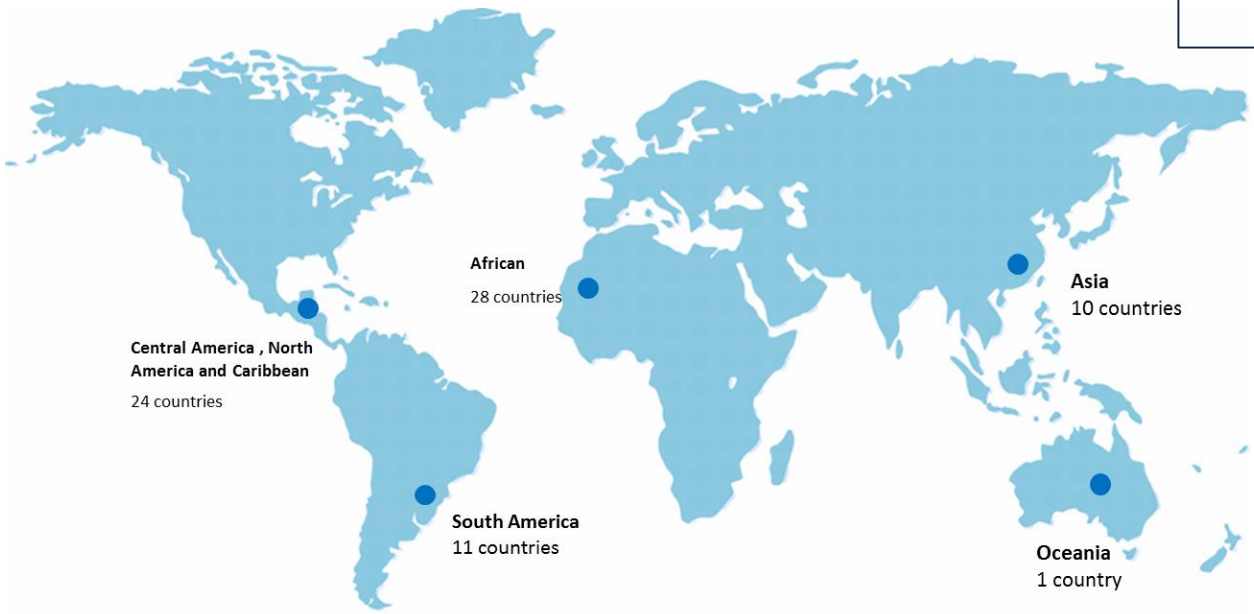
Preliminary - Comparison from Module 2 – 5 - Content

3.2.R - Regional Information
3.2.R.1 Transport qualification
3.2.R.2 Production Documentation and Hemoderivative Quality Control
3.2.R.3 Analytical Comparison - Biological
3.2.R.4 Production Order (s) of the lot (s) / biolote (s)
3.2.R.5 Partial validation of the analytical methodology carried out by the Importer
3.2.R.6 Detail of control strategy
3.2.R.7 Phytotherapy in association
3.2.R.8 Post-Registration

ANVISA_International Council of Harmonization ICH

- ❑ CTD Harmonization – Impact in prequalified vaccines supply
- ✓ WHO PROMOTES DEVELOPMENT OF REGULATORY AGENCIES
- ✓ Besides the prequalification, some countries asks local registration

74 Countries



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Bio-Manguinhos Initiatives to adopt CTD Format

- ❑ Experience from Tech Transfer process
- ❑ Qualification of the Regulatory Affair Group
- ❑ Perform a pilot – Adapt a Dossier in RDC 55/2010 format using the CTD format
- ✓ Consider the granularity in the files organization
- ❑ Evaluation of CTDs electronic system available in the Market

Bio-Manguinhos Initiatives to adopt CTD Format

- Training of professionals involved in Technological Development in CTD requirements

	Pre clinical	Clinical Trials	Tech Transfer	TOTAL
Bacterial vaccines	1	1	2	4
Viral vaccines	5	1	4	10
Biopharmaceuticals	1	1	5	7
IVDs	4	-	2	6
TOTAL	**11**	**3**	**13**	**27**

Challengers_ Bio-Manguinhos to adopt CTD Format

- More Complex (even when compared to PSF Format – WHO)
- Adjust how information is generated – Production, Quality Assurance, Quality Control, Validation data, clinical data.
- More detailed information related to clinical and preclinical Information
- Structure – Granularity Level
- Time of acquisition and implementation of the electronic System

Challengers_ Bio-Manguinhos to adopt CTD Format

- Old vaccines

Case: Yellow Fever

- Established in the late 1930,
- It has been used worldwide and has shown as essential instrument for the control of Yellow Fever disease.
- The 17DD Yellow Fever vaccine, derived from Yellow Fever 17D strain developed at the Rockfeller Foundation, N.Y.
- In 1937, after reception in Brazil of 17D and 17DD strain, the parameters of production of this were further developed and several large field trials were conducted.
- The final production procedure was established at Oswaldo Cruz Foundation. Since then, this vaccine has been continuously produced and used.
- In Brazil, the massive and routine immunization, made possible the elimination of the urban Yellow Fever in 1942.
- Several clinical trials have also demonstrated that the 17DD Yellow Fever vaccine presents 98% or higher immunogecity and a low reactogenicity profile,

Challengers_ Bio-Manguinhos to adopt CTD Format

Case: Yellow Fever

According to CTD Format, the manufacturer have to present clinical and preclinical information.

Some examples:

- Carcinogenicity
- Reproductive and Developmental Toxicity
- Antigenicity
- Immunotoxicity
- Reports of Studies Pertinent to Human PK

Challengers_ Bio-Manguinhos to adopt CTD Format

Alternative to old vaccines:

- Use of historical data
- Product Quality Review
- Historical of change control
- Pharmacovigilance data
- Epidemiological Impact
- Publications

Thank you

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