Scientific and Regulatory Considerations for Rare Diseases' Therapies: An Overview from Brazil

UCSF-Stanford CERSI Immersion Program
Stanford University – April 15, 2019
Acknowledgements – Case Study

- Daniela Sturzenegger
- Deepti Gupta
- Douglas Souto
- Jacqueline Tran
- Juliana Ortiz
- Katia Alves
- Lara Pereira
- Lais Rocha
- Natalia Khuri
- Nadia Ayad
- Obi Okafor
- Raphael Sanches
- Telma Caldeira
- Terrence Blaschke
Outlines

Part I: Brazil as a Potential Market for Clinical Trials

• Brazilian Scenario for Clinical Trials
• Brazil’s Regulation for Clinical Trials - Rare Diseases

Part II: The New Regulatory Pathway for Rare Diseases in Brazil

• Registration of Drug Products in Brazil – An Overview for Rare Diseases
• Understanding of Rare Diseases and their impact
• The new Accelerated Pathway for Rare Diseases and its milestones (RDC nº 205/2017)
• Results for the Accelerated Pathway in 2018
• What are the future directions and opportunities?
Brazil as a Potential Market for Clinical Trials

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Disclaimer

I am an independent contributor. The content of the following presentation is a summary of my professional experience and does not represent any of the Institutions hereby mentioned.
Clinical Trials in Brazil - Rare Disease

Genetic Diversity  Access  Time
Clinical Trials in Brazil - Rare Disease

Genetic Diversity

Access

Time
Population and Genetic Diversity

- Brazil is the Fifth most populous country in the world;
- The Biggest Country in the Latin America;

Source: By Max Roser - ourworldindata.org
Population and Genetic Diversity

- The immigration of different people during centuries of colonization led to heterogeneous miscegenation of Brazilian population;
- European, African, and Brazilian Native Amerindians

Genetic diversity is a large pool of potential volunteers.
Genetic Diversity

In the 1950s and 1960s Brazil had a high number of consanguineous marriage.

- High Prevalence of Mucopolysaccharidosis Type 6 at Monte Santo-BA (1:5000 against 1:350000 in other countries)
  - There is only one drug available to treat MPS-6, already approved by Anvisa;
  - There are 3 new technologies in Phase 1 and 2 but none of these studies are being conducted in Brazil.
Genetic Diversity

- High Prevalence of Spinocerebellar Ataxia Type 3 (Machado-Joseph disease) in south of Brazil (1:30,000)
  - There is no treatment for this disease, just for some symptoms;
- High Incidence of Osteogenesis Imperfecta (more than 12,000 people affected)
  - There is no treatment for this disease, just for some symptoms;

There is a potential market for these diseases in Brazil
Clinical Trials in Brazil - Rare Disease

Genetic Diversity

Access

Time

Claudia Nora, Ph.D - Research Regulatory Specialist
Reference Centers

Health care is a Constitutional Right. Currently 75% of the population depend on the Public Healthcare System.

In 2014, the Brazilian government created an ordinance (199/2014) that:
- Establishes guidelines for people with rare diseases;
- Provides health care;
- Guarantees access to the diagnostic and therapeutic sources available;
- Qualifies health care professionals;

Attractive place to recruit patients
Patient Associations

- Support for patients and their families;
- Participation in political discussion about Rare Disease;
- Connect People;
- Provide information to the population, family, and professionals.
Clinical Trials in Brazil - Rare Disease

Genetic Diversity

Access

Time
Process to perform Clinical Trial - Rare Disease
RDC 205/2017

Non-Clinical Studies → Clinical Studies

- DDCM - ANVISA: 90 days
- Institutional IRB (CEP): 30 days
- National IRB (CONEP): 90 days
CONEP has improved their process in the last years, with the implementation of new resolutions, guidelines and guidances.

* average timelines for CONEP’s first opinion letter

**Competitive regulatory pathway**
Clinical Trials in Brazil - Rare Disease

Genetic Diversity

Access

Time
The New Regulatory Pathway for Rare Diseases in Brazil

Ms. Alana Galeno and Ms. Gabrielle Pereira
Brazilian Health Regulatory Agency (ANVISA)
The opinions expressed in this presentation are the authors own and do not reflect the view of the Brazilian Health Regulatory Agency (ANVISA). They are a result of the discussions undertaken during the CERSI Immersion Program for the proposed case-study.
With the recently enacted resolution for accelerated pathway of approval for rare diseases and the increasing number of applications submitted in the country, **how to effectively guarantee expedited approval without compromising quality, safety and efficacy?**
Brazil at a Glance

- Population: around 210 millions
- 26 states and the Federal District
- $U.S. 17 billion Industrial pharmaceutical market in Brazil in 2018
- 5th Pharmaceutical Market in 2022

SUS – National Public Health System:
“Health as a citizen’s right and the government’s responsibility”: free and universal access to health care.
What is Rare Disease?

Rare Disease is a *life-threatening or chronically debilitating condition that affects a small number of people.*

- **USA - Orphan Drug Act**
  - Affects less than 200,000 people in the U.S.
  - 1983

- **European Union**
  - Low prevalence (less than 5 per 100,000)
  - 1999

- **Japan - Medicines Act**
  - No more than 50,000 people in the country
  - 1993

- **Brazil - Ministerial Order 199/2014**
  - One that affects up to 65 per 100,000 individuals
  - 2014

**National Policy of Integral Care to People with Rare Diseases**
6,000 to 8,000 distinct rare diseases are estimated to exist in the human population.

About 80% of rare diseases are of genetic origin and 20% of infectious, viral or degenerative causes.

13 million Brazilians live with these diseases and for 95% have treatment with palliative drugs, 3% surgical treatment and 2% treatment with orphan drugs (able to interfere in the progression).

Brazilian Health Regulatory Agency (Anvisa)

Regulatory Agency: administrative independence and financial autonomy

- 20 years since its creation (Law 9.782/1999)
- Linked to the Ministry of Health
- Board of Directors – 5 Directors named by the President
- Anvisa has competency to issue regulations related to health surveillance subjects – Resolution of the Board of Directors (RDC)
To protect and promote the health of the population, by intervening on the risks associated with manufacturing and use of products and services subject to health regulation, in a coordinated and integrated action within the National Health System (SUS).
Scope of Anvisa’s Regulations

- Foods
- Cosmetics
- Sanitizer
- Tobacco
- Pesticides
- Health Service
- Medical devices
- Official Laboratories
- Blood, Tissues and organs
- Pharmacovigilance
- Advertisement
- Ports, airports and borders
- International affairs
- SNVS coordination
Accelerated Pathway of Approval for Rare Diseases

RDC 205/2017 - Establishes special procedure for clinical trials authorization, GMP (Good Manufacturing Practices) and registration of new medicines for treatment, diagnosis or prevention of rare diseases

Published December 28, 2017 and effective on February 26, 2018.

Define the eligibility criteria for this special pathway and which are the special requirements.

- Mandatory pre-submission meeting
- Clinical Trial Authorization expedited procedure
- Drug Product Registration expedited procedure
- CTD format for dossier submission (ICH M4 Guideline)
- GMP Certification deadline: 120 days
Special Procedure for Registration of Rare Diseases Drug Products

*DDCM – Drug Clinical Development Dossier*
Special Procedure for Registration of Rare Diseases Drug Products

*DDCM – Drug Clinical Development Dossier*
DDCM final decision takes up to 90 days

- Pre-submission request
- Pre-submission meeting
- DDCM Submission
- Notification requirement
- Compliance information
- Final decision

60 days
30 days
30 days
30 days

Company’s actions
Anvisa’s actions
Special Procedure for Registration of Rare Diseases Drug Products

Pre-clinical → Phase 1 → Phase 2 → Phase 3 → Launch/Post-Launch

DDCM* Submission (IND) → Registration Dossier (BLA or NDA)

*DDCM – Drug Clinical Development Dossier
Registration Dossier final decision takes up to 135 days

60 days
Pre-submission request
Pre-submission meeting
60 days
Notification requirement
45 days
Compliance information

30 days
30 days

Registration Dossier

Company’s actions

Anvisa’s actions

Final decision

ANVISA
Agência Nacional de Vigilância Sanitária
CLINICAL STUDIES
- Presentation of phase II studies completed and phase III studies in progress, or without the presentation of phase III clinical studies, when the execution of these studies is not feasible.

QUALITY CONTROL
- Imported drug products: waiver of quality control tests done in Brazil, if the quality control is done by the manufacturer of the drug and if it is presented summary report of qualification of operation of the transport system.
- Submission of a registration request can be accepted study of long-term stability in progress.
RDC 205/2017 – Important Milestones for Registration

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*Signing of a term of commitment between Anvisa and the requesting company.*
RDC 205/2017 – Important Milestones for Registration

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**The meeting request for pre-submission must be held within 60 days after the first registration request in another regulatory authority.
17 clinical trials approved for rare diseases in Brazil on the year of 2018

Time for conclusion varied between 7 and 164 days

Sources: DOU (http://www.in.gov.br/web/guest/inicio) and Anvisa’s website (http://portal.anvisa.gov.br/)
Average time (in days) of 2018 Registration Dossiers

- **New - Non prioritized**
  - Time in Line: 83 days
  - Anvisa’s Time: 432 days
  - Company's Time: 183 days
  - Total: 698 days

- **New - Rare diseases**
  - Time in Line: 124 days
  - Anvisa’s Time: 35 days
  - Company's Time: 231 days
  - Total: 290 days

Total average time for all dossiers: 988 days
Results of the Prioritization since February 2018

7 new drug products approved in 2018 for rare diseases

Sources: DOU (http://www.in.gov.br/web/guest/inicio) and Anvisa’s website (http://portal.anvisa.gov.br/)
## 2018 - New Registered Drugs

<table>
<thead>
<tr>
<th>Brand Name (Name of Drug)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavencio® (avelumab)</td>
<td>Merkel cell carcinoma, metastatic</td>
</tr>
<tr>
<td>Brineura® (cerliponase alfa)</td>
<td>Neuronal ceroid lipofuscinosis, type 2</td>
</tr>
<tr>
<td>Cabometyx® (cabozantinib levomalate)</td>
<td>Advanced renal cell carcinoma</td>
</tr>
<tr>
<td>Calquence® (acalabrutinib)</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Kalydeco® (ivacaftor)</td>
<td>Cystic fibrosis, type R117H mutation</td>
</tr>
<tr>
<td>Mepsevii® (vestronidase alfa)</td>
<td>Mucopolysaccharidosis vii (Sly syndrome)</td>
</tr>
<tr>
<td>Orkambi® (lumacaftor + ivacaftor)</td>
<td>Cystic fibrosis, type F508del mutation on CFTR</td>
</tr>
</tbody>
</table>

Sources: DOU (http://www.in.gov.br/web/guest/inicio) and Anvisa's website (http://portal.anvisa.gov.br/)
Future Directions and Opportunities

How to effectively guarantee expedited approval without compromising the state-of-the-art evaluation of quality, safety and efficacy of new medicines?

- Better and faster collaboration between Anvisa and other health regulatory agencies
- Training and fostering regulatory science research
- Leverage the innovative research produced in Brazil
How do you find rare disease info on Anvisa site?

You can find all information about the administrative procedure for rare disease protocols on the links below (all in Portuguese):


- Rare Disease Applications still awaiting for analysis: [https://consultas.anvisa.gov.br/#/filas/](https://consultas.anvisa.gov.br/#/filas/)

Thank you!
Obrigado!

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