



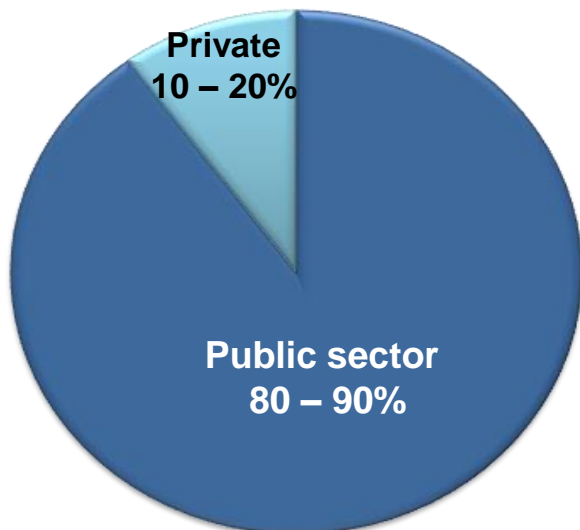
Instituto Butantan

2013

BRAZILIAN MARKET FOR VACCINES

IT IS A PUBLIC MARKET

Estimated market share in Brazil for vaccines



DEMAND

- ❑ The Brazilian market for vaccines is characterized by being linked to the public demand
- ❑ It is estimated that between 85% and 90% of sales of vaccines in Brazil are made to the MoH
- ❑ The value of government purchases is determined by the annual budget of the National Immunization Program (PNI)
- ❑ Since it was founded, the PNI has enabled the expansion of coverage from **20%** in 1970 to over **95%** in 2011

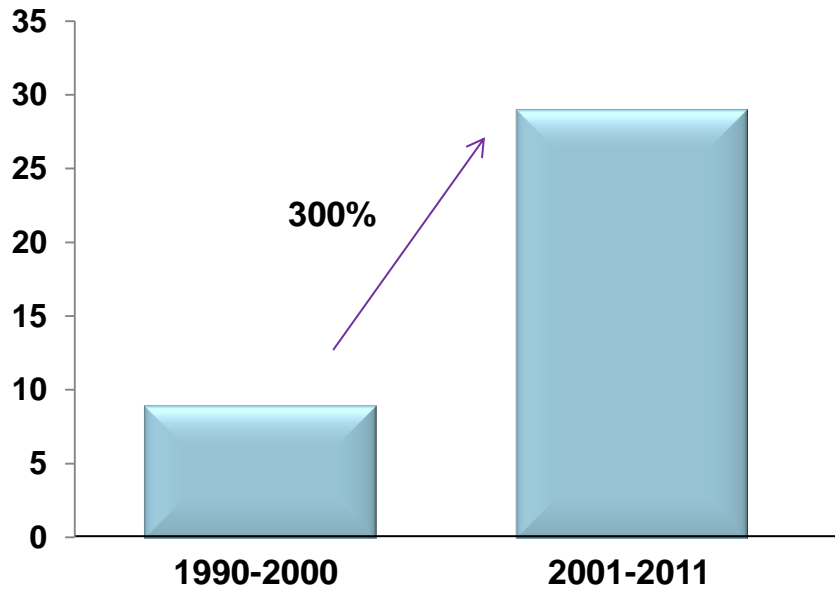
SUPPLY

- ❑ The supply of biopharmaceuticals in Brazil, as the demand, is mostly public
- ❑ The main producers are
 - ✓ Fiocruz (Bio-Manguinhos), connected to the MoH
 - ✓ Butantan, connected to State Department of Health of São Paulo
- ❑ Both institutions account for **93%** of the units of vaccines

OUR IMPACTS

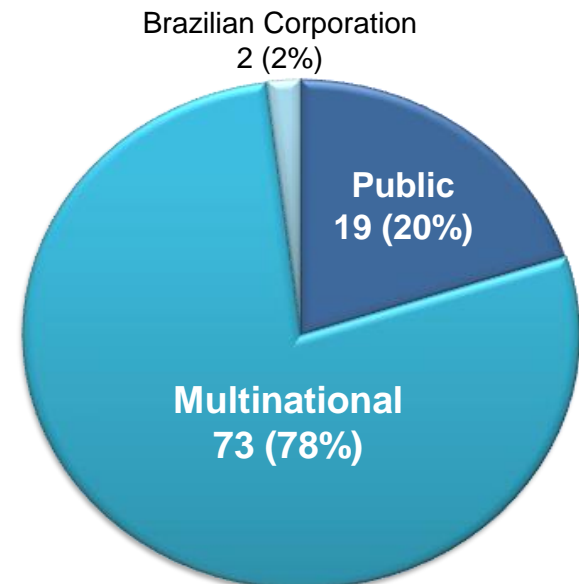
DEPOSIT REQUESTS MADE BY BRAZILIAN LABORATORIES IN INTERNATIONAL PATENT OFFICES

Patents vaccines required in international offices



Source: Espacenet (2011)

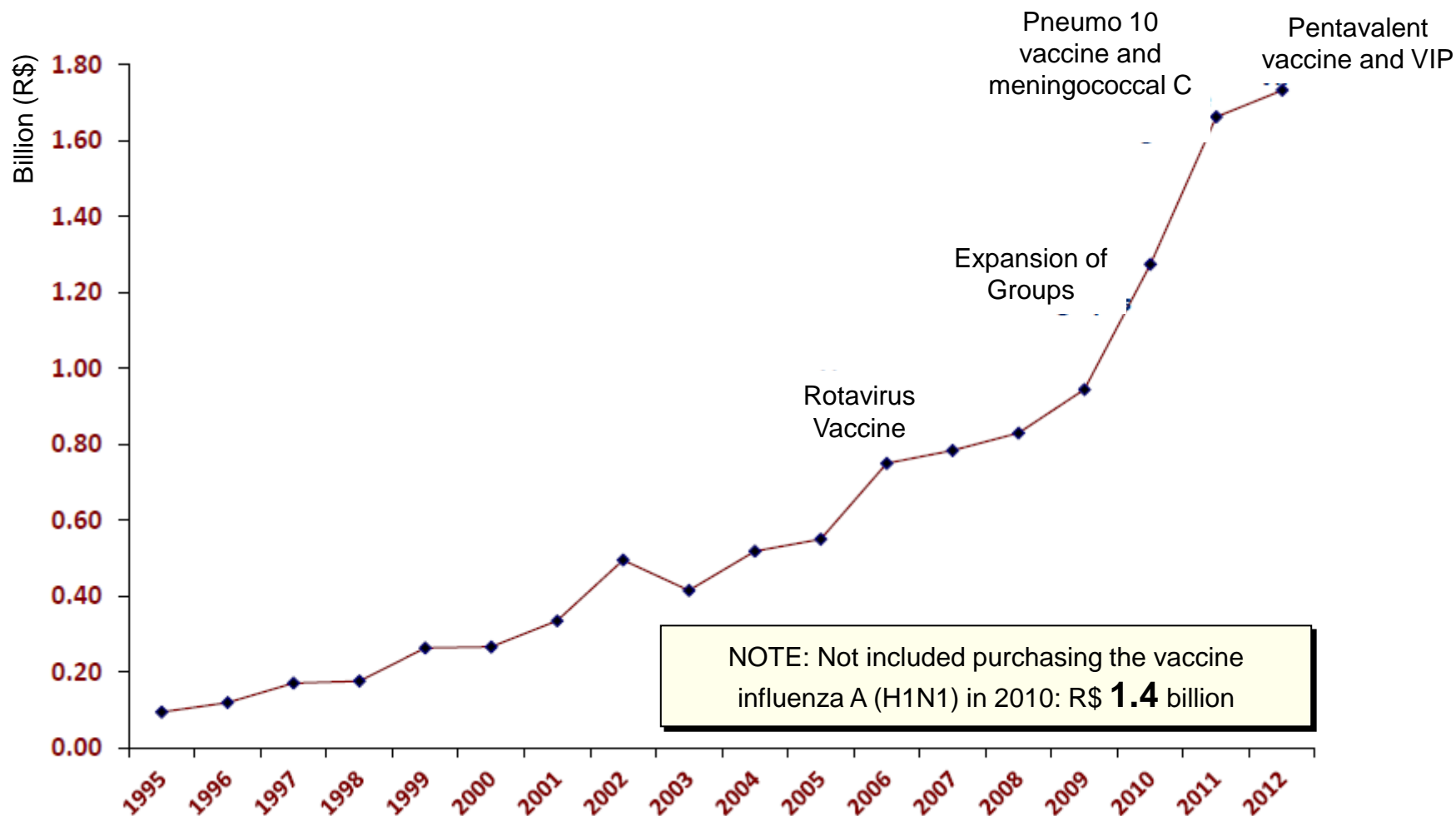
Number of registered vaccines at ANVISA (94)



Source: Anvisa (2011)

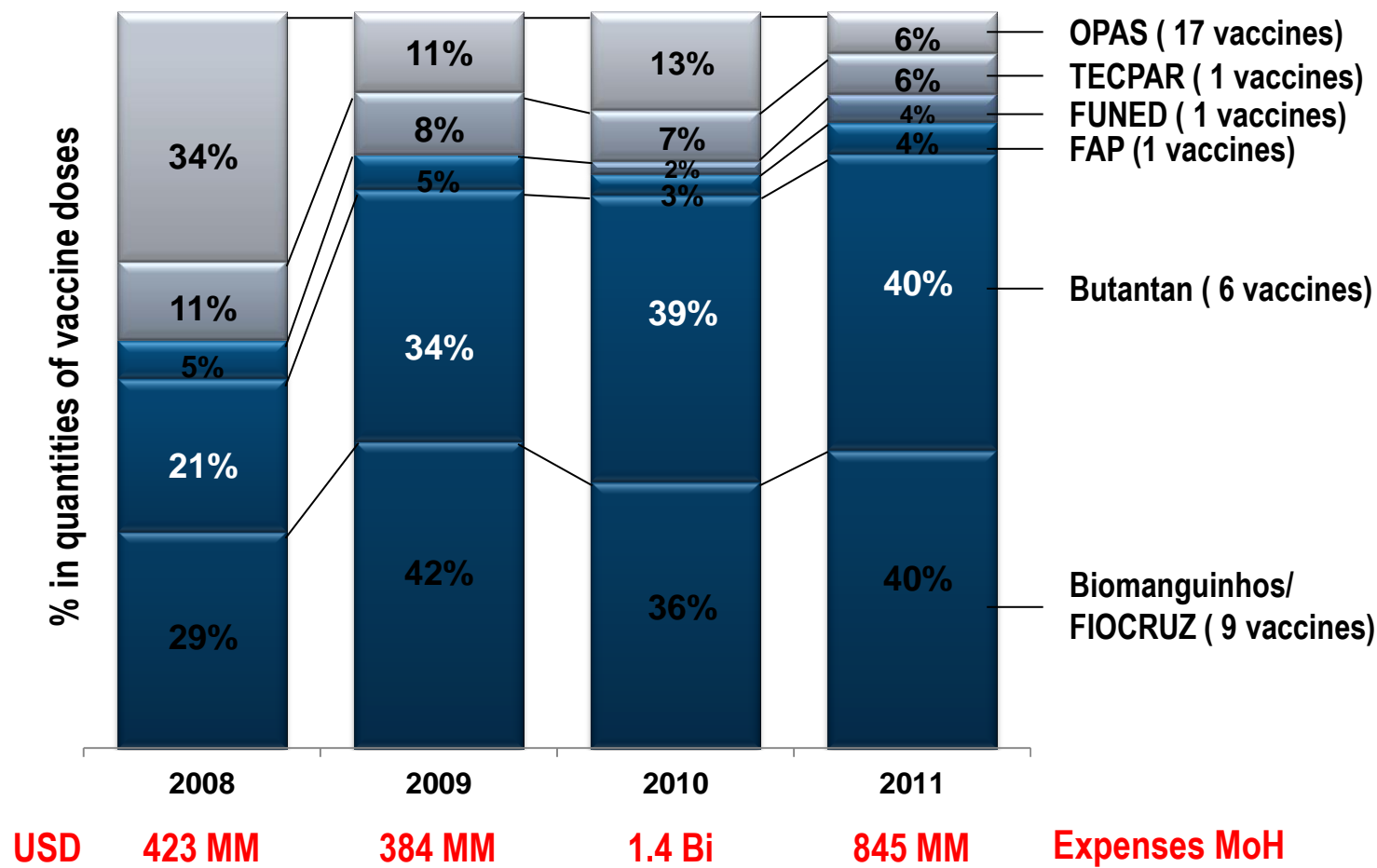
BUDGET PNI (1995 – 2012)

WITH THE FLU VACCINE, VACCINES BUDGET EXCEEDS U\$ 1 BILLION



BUTANTAN IS ONE OF THE MAIN PUBLIC PRODUCER

DOSES OF VACCINES ACQUIRED BY THE MINISTRY OF HEALTH



IN BRAZIL:

THERE ARE THE VACCINES OF SCHEDULE AND VACCINATION CAMPAIGNS

Vaccines Schedule

Newborns, children and pre-teens

- | | |
|--------------------------------|--|
| 1. BCG (Tuberculosis) | 7. Yellow fever |
| 2. Hepatitis B | 8. Measles, Mumps and Rubella (MMR) |
| 3. Penta (DTP + Hib + Hep B) * | 9. Difteria, Tetanus and Pertussis (DTP) |
| 4. OPV (Oral Polio) | 10. Meningitis C |
| 5. IPV (Polio IM) | 11. Pneumococco 10 |
| 6. VHR (Oral rotavirus) | 12. Influenza |

Adolescents and adults

1. Hepatitis B (29 years)
2. dT (Tetanus and Difiteria)
3. Yellow fever
4. Measles, Mumps and Rubella (MMR)

Elderly (+ 60 years)

1. Influenza
2. Pneumococco (PPSV23)

Vaccination Campaigns

- **Influenza – 44 million doses per year**
 - ✓ Pregnant women, the elderly, indigenous peoples, children, health care workers, prisoners
- **Polio - OPV (1x per year)**
- **Multivaccination (specific updates)**
- **Measles and Rubella**
 - ✓ Every 4 years or according to the epidemiological situation

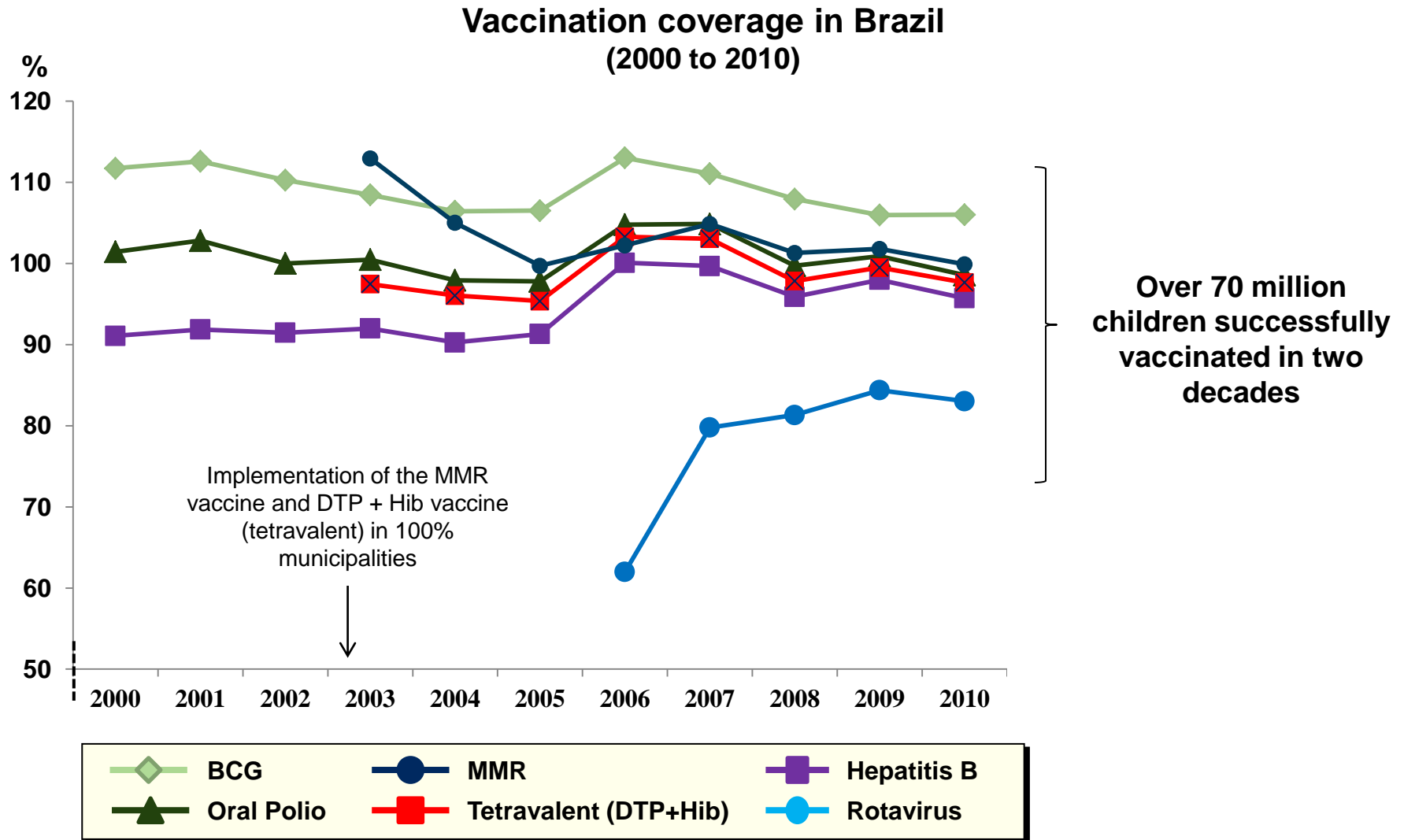
HOW THE VACCINES ARE INTRODUCED IN BRAZIL

COST-EFFECTIVENESS FOR INTRODUCTION OF NEW VACCINES IN THE PNI

Epidemiological	When morbidity and mortality of the disease are high
Immunological	High efficiency (above 70%) and lasting immunity
Local production	<p>The production must be by public laboratories - to guarantee the supply and price</p> <p>PNI only introduces new vaccine if it is produced in Brazil</p>
Logistics	The inclusion of a new vaccine requires an investment plan
Price	The introduction of new products depends on pricing

OUR IMPACTS

Vaccination coverage by type of vaccination in the child's

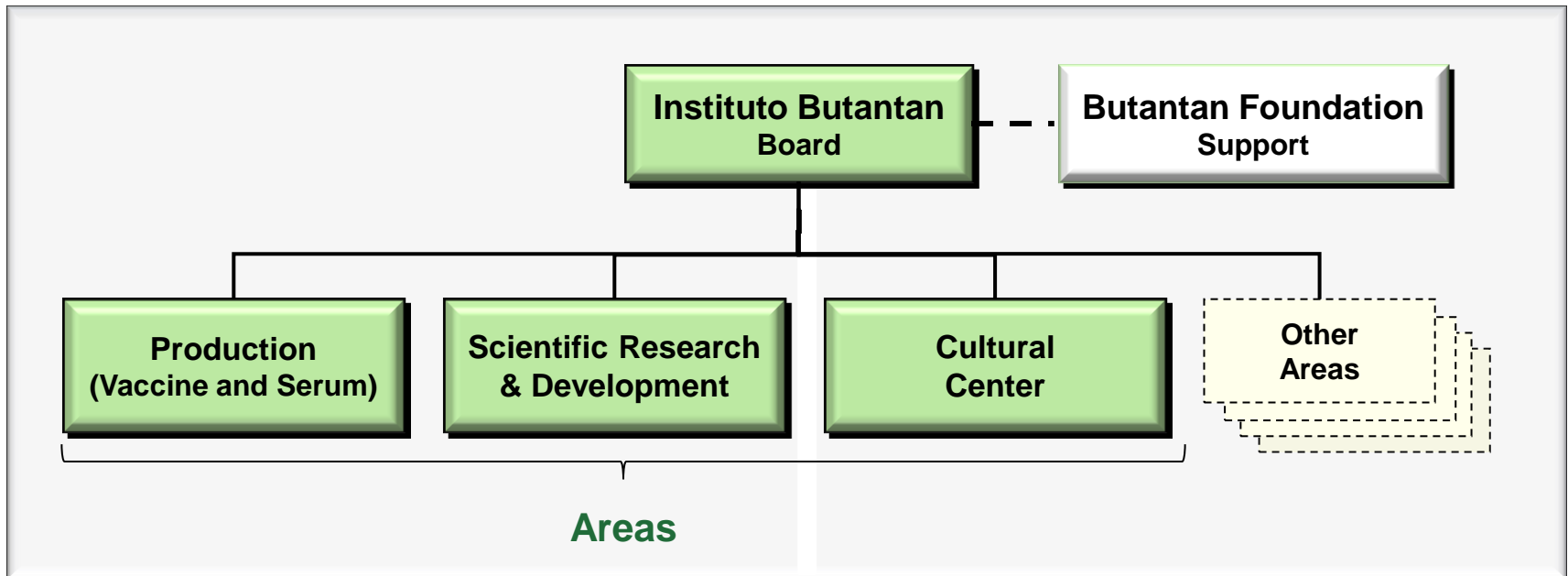


BUTANTAN – A PUBLIC INSTITUTION OF THE STATE GOVERNMENT OF SÃO PAULO

- ❑ In 1901 Butantan was established to produce serum against the bubonic plague
 - ✓ Vital Brazil, the first director, investigated antivenoms against snake bites
- ❑ Currently, Butantan is one of the main public producer of vaccines, antivenoms, antitoxins in Latin America
 - ✓ Fully dedicated to develop scientific research and production of immunobiological products for public health



MACRO ORGANIZATIONAL STRUCTURE



- **~1.820 Direct Employees**
 - ✓ Public Servants 770 (42%)
 - ✓ Foundation's Employees 1053 (58%)
- **~100 Outsourced employees**

INDUSTRIAL COMPLEX - PRODUCTION

■ 7 Main Industrial Plants

- ✓ Anaerobic vaccines (tetanus and botulinic) and Anatoxin Purification
- ✓ Aerobic Vaccine (Diphtheria and Pertussis)
- ✓ Hepatitis
- ✓ Influenza
- ✓ Rabies
- ✓ Blood Products (under construction)
- ✓ Control, Serums, Formulation and Filling

■ 6 Pilot Plants

- ✓ Dengue / Rotavírus (Under Construction)
- ✓ Recombinant (BCG)
- ✓ Monoclonal Antibodies
- ✓ Influenza (H5N1)
- ✓ Blood Products



SCIENTIFIC RESEARCH & DEVELOPMENT LABORATORIES

- ~21 scientific labs
 - ~180 Researchers
 - ✓ 85% are PhD
 - 1 Biotechnology Center
 - ✓ Multiple laboratories
 - 1 Hospital (10 hospital beds)
 - 1 Central Animal Facility
-
- Training programs (PAP)
 - Graduate studies in Toxinology
 - Masters and PhDs



CULTURAL CENTER

- 4 Museums
- ~300K visitors/year
- An area with ~ 800.000 m²
- Preserved green area



HISTORICAL MUSEUM



MUSEUM OF MICROBIOLOGY



BIOLOGICAL MUSEUM



PRODUCTS FOCUS

Vaccines

- **Schedule Vaccines**
- *Vaccines under clinical trials*
- *Vaccines under development*

Hyperimmune Sera

- **Antivenoms**
- **Antitoxins**

Blood Products

- *IgG*
- *Coagulations factors*
- *Albumin*
- *Others proteins*

Other Bioproducts

- *Lung surfactant*
- *Monoclonal antibodies*

Legend:

Produced

Under development

CURRENTLY PRODUCTS OF BUTANTAN – SCHEDULE VACCINES AND SERA

Vaccines (6 products)



Vaccine
DTP



Pediatric Vaccine
DT



Adult Vaccine
dT



Vaccine
Rabies



Recombinant Vaccine
Hepatitis B



Vaccine
Influenza (Flu)

Antivenom, Antitoxins and Antiviral (13 products)

Snakes AV (5 products)



Bothrops Antivenom
(Pit viper)



Crotalus Antivenom
(rattlesnake)



Antivenom
Bothrops-Crotalus



Lachesis Antivenom
(Bushmaster)



Micrurus Antivenom
(Coral snake)

Others (8 products)



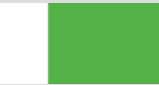
Antivenom
Scorpion



Antivenom
Spider / Scorpion



Antivenom
Lonomia Caterpillar



Serum Anti
Tetanus



Serum Anti
Diphtheria

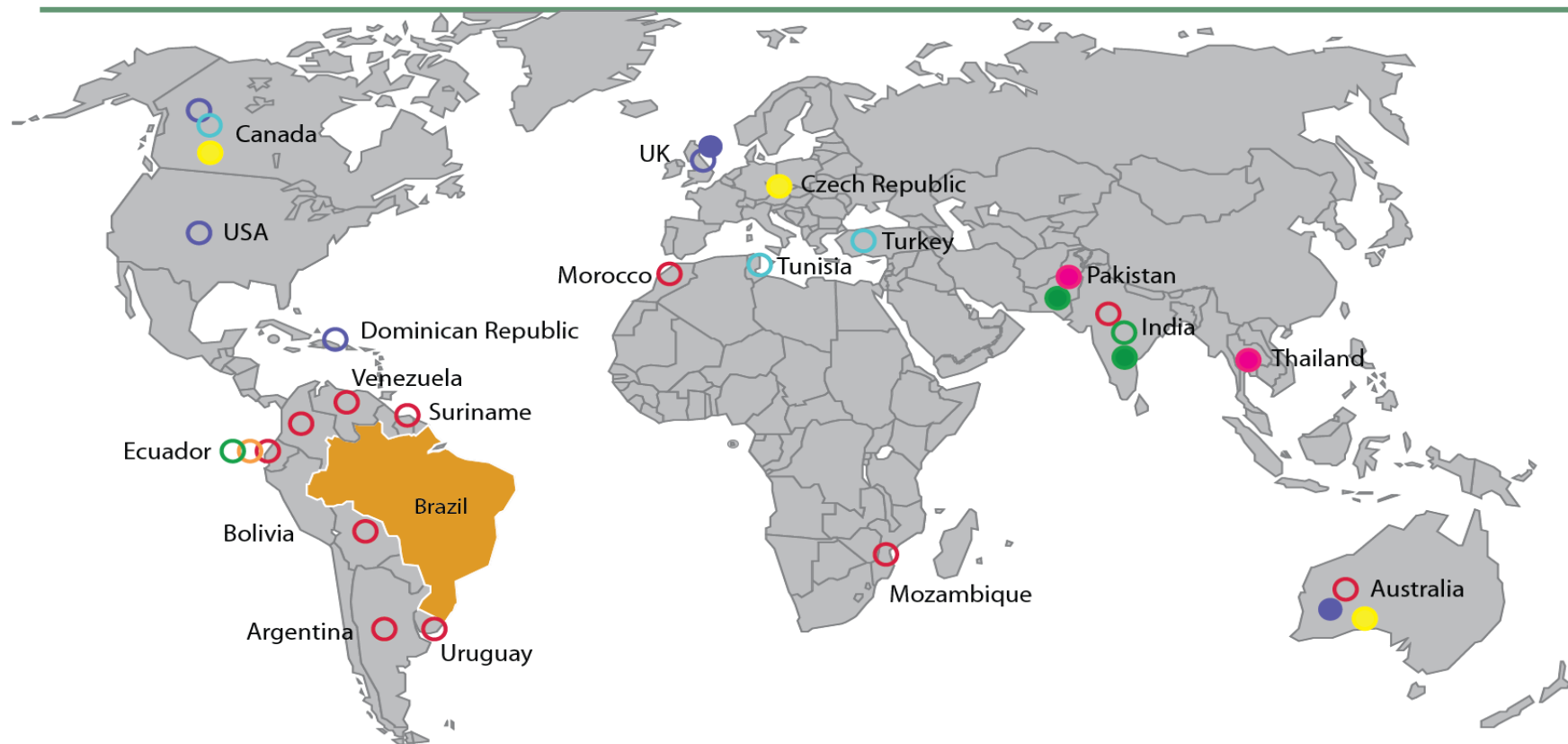


Serum Anti
Rabies



Serum Anti
Botulism AB & E

EXPORTING PRODUCTS



ANTIVENOMS AND ANTITOXINS

- Blue circle: Diphtheria Antitoxin
- Cyan circle: Botulism Antitoxin
- Red circle: Snake and Scorpion Antivenoms
- Orange circle: Tetanus Antitoxin
- Green circle: Rabies Antitoxin

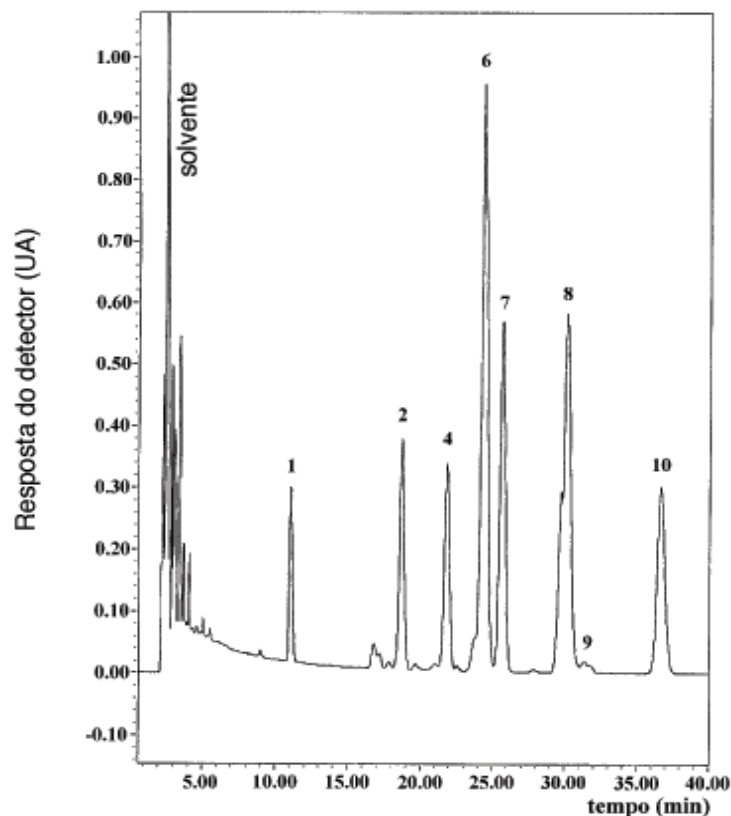
VACCINES

- Dark blue circle: Anti diphtheria
- Dark green circle: Anti rabies
- Yellow circle: Hepatitis B
- Pink circle: DTP, DT

SCREENING OF BIOACTIVE COMPONENTS OF POISONOUS ANIMALS

Venom Composition (Transcriptomics and Proteomics)

Pharmacological activities



- ❑ ANALGESICS
- ❑ ANTI- INFLAMMATORY
- ❑ ANTICOAGULANTS
- ❑ ANTITUMOR
- ❑ ACTION IN THE NERVOUS SYSTEM
- ❑ ANTIVENOMS
- ❑ ANTIHIPERTENSIVE

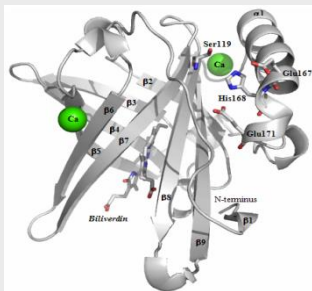
PATENTS – SAMPLES

OVER THAN 50 PATENTS

1

LOPAP (4 patents)

- Prothrombin activator,
- defibrinogenating/ antithrombotic agent
- kit for diagnosis of dysprothrombinemias
- anti-apoptotic activity



Lonomia obliqua

TICKS' SALIVARY GLANDS (2 patents)

- A new anticoagulant and anti-tumoral agent
- Microarray analysis



Amblyomma cajennense

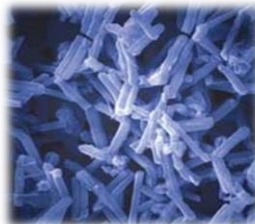
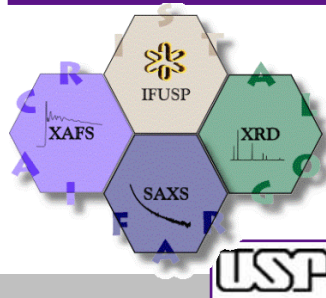
3

4

2

IMMUNOGENIC COMPLEX FORMED BY VACCINAL ANTIGENS
ENCAPSULATED BY NANOSTRUCTURED MESOPOROUS SILICA

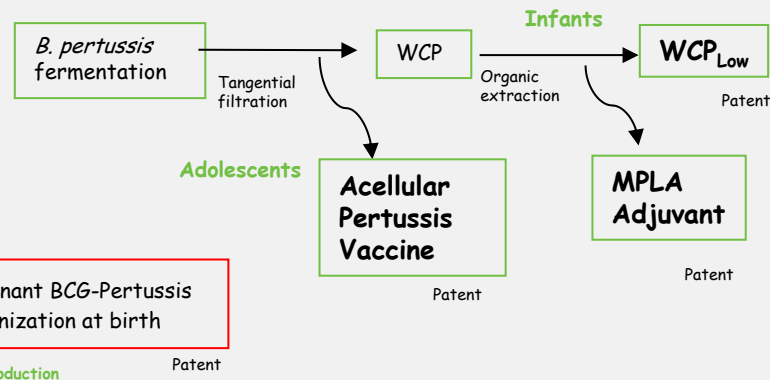
CRISTALOGRAFIA
LABORATÓRIO



New developments in Pertussis Vaccines with Appropriate technologies

Whole Cell Pertussis Vaccine

Low LPS content- Whole Cell Pertussis
less reactogenic - low cost



BUTANTAN'S FARM



50 Km from São Paulo

1.250 hectares

~ 800 horses

AGENDA

»» BRAZILIAN VACCINE INDUSTRY

»» INSTITUTO BUTANTAN

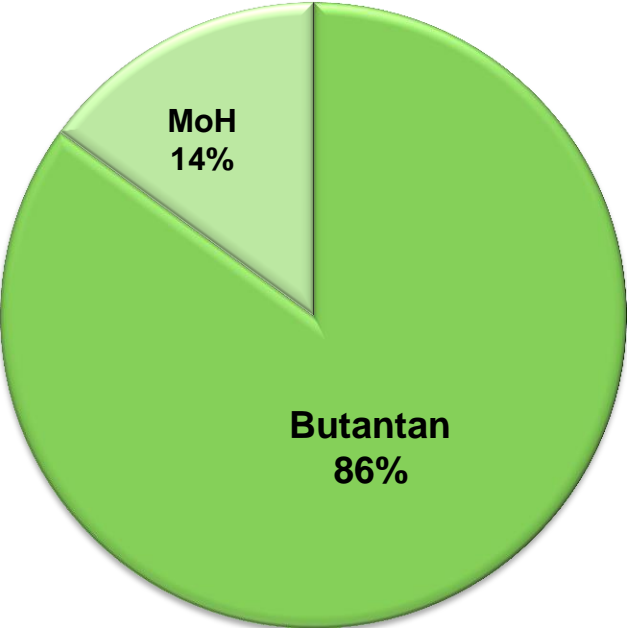
»» **OUR PROJECTS**

Actions for qualification in cGMP processes

- ❑ Renovation in all factories to WHO and ANVISA certification
- ❑ Re-structuring of the Quality System in accordance with ICH Q10
- ❑ Expansion of the workforce in the areas of Quality Assurance and Control
- ❑ Review of all Water System - WFI and PW
- ❑ Review of all HVAC Systems
- ❑ Execution of validations Analytical Methodologies, Cleaning and Processes
- ❑ Enforcing Validation Filtration sterilants
- ❑ Implementation of the Computerized System Validations
- ❑ Quality Training organized by PATH Vaccine Development Program
- ❑ Treinamentos de Qualidade organizado pelo PATH Vaccine Development Program

Investments in cGMP processes

Distribution of Expenditures and Investments



Amounts of Spending and Investment

ESTIMATE OF INVESTMENTS GMP / PRODUCTION		
	QTDE.	VALOR (R\$)
Services	--	30.000.000
Equipment	170	80.000.000
Construction & Remodeling	40	147.000.000
TOTAL (R\$)	--	257.000.000

WHAT DO WE WANT TO DO?

Presentation and discussion of vaccines projects

Area	Vaccines Projects – under development ¹
Vaccines - Research and improvement	<ul style="list-style-type: none">▪ Pertussis_{low}▪ Recombinant onco BCG▪ Silica nanostructure mesoporous – vaccine antigens encapsulated▪ Adjuvant <i>BpMPLA</i>
Vaccines - Collaborative development	<ul style="list-style-type: none">▪ Dengue (tetravalent)▪ Rotavirus (pentavalent)▪ <i>Streptococcus pneumoniae</i> (cellular - SPWCV)▪ BCG-Pertussis
Vaccines – Basics research and development	<ul style="list-style-type: none">▪ Leptospira
Vaccines – Technology transfer	<ul style="list-style-type: none">▪ Vaccines approved<ul style="list-style-type: none">✓ Hepatite A (Merck)✓ HPV (Merck)✓ Monoclonal (Libbs/Chemo)✓ dTp acelarar

¹ Not exhaustive

POTENTIAL PORTFOLIO WITH MORE THAN 20 NEW PRODUCTS - INNOVATION ...

Nº	Productos	Description
1	HEMODERIVATIVES	Production of IgG, factor VIII, IX, Albumine and other products
2	DENGUE VACCINE	Attenuated tetravalent Vaccine (sorotypes DEN1, DEN2, DEN3, DEN4)
3	ROTAVIRUS VACCINE	Attenuated Pentavalent Vaccine (sorotypes G1, G2, G3, G4, G9)
4	PERTUSSIS LOW VACCINE	B. pertussis whole cell with lower content of LPS
5	ADJUVANT <i>Bp</i> MPLA	BpMPLA derived from LPS of B.pertussis to be combined to different vaccines
6	RECOMBINANT BCG	Bladder cancer treatment
7	BCG-PERTUSSIS + HEP B	Vaccine for neonates
8	MONOCLONAL ANTIBODIES	Biosimilars (rituximab, bevacizumab, cetuximab, infliximab)
9	DTP _{LOW} -HEPB-HIB	Pentavalent vaccine for the MoH
10	DTP _{LOW} -HEPB-HIB-IPV-MENC	Heptavalent vaccine for the MoH
11	HEPATITIS B	Hepatitis B vaccine for > 50 years old and imunodefficiency people
12	LEPTOSPIRA VACCINE	Purified recombinant protein of Leptospira expressed in Escherichia coli strain
13	LUNG SURFACTANT	Industrial production of the surfactant from porcine origem
14	SILICA (SBA-15)	Immunogenic complex from silica (Adjuvant for vaccines administered orally)
15	AMBLYOMIN-X	Anti-cancer
16	CROTALPHINE	Potent analgesic drugs from animal venoms. Long-lasting analgesic (2-5 days)
17	LOPAP	Prothombin Activator, Anti-apoptotic activity and pharmaceutical formulations
18	CROTAMINA	Treatment of dysfunctions based genetic materials, such as DNA and RNA
19	PNEUMOCOCCAL	Inactivated non-encapsulated pneumococcal whole cell
20	NECATOR - SCHISTOSSOMA	Cloning, expression and purification of recombinant proteins from E.coli and Yeast
21	BEE'S ANTIVENOM	Bee's antivenom



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