Graduate Institute/Global Health Centre
Knowledge Network for Innovation and Access

Local production of essential medicines in Brazil

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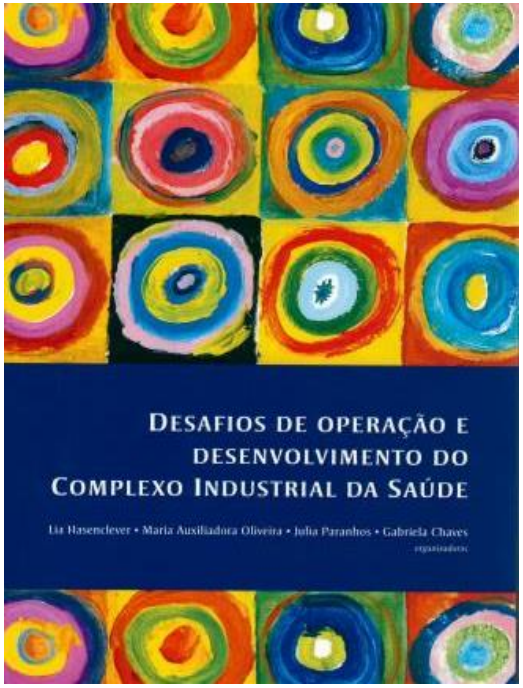
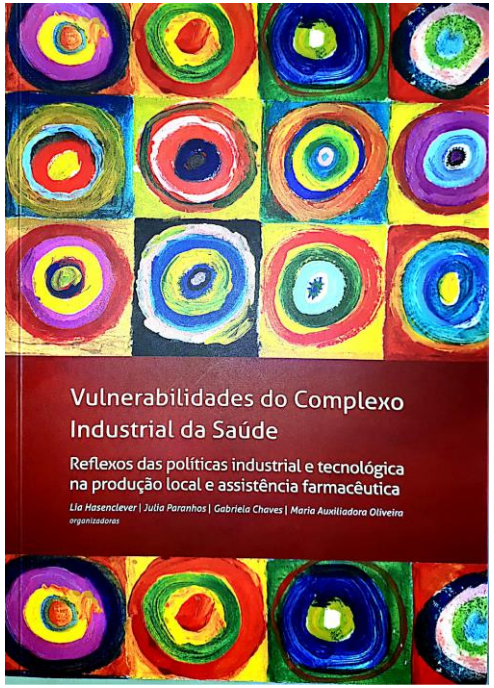
Research background

- Department of Medicines Policy and Pharmaceutical Services (NAF), Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation (ENSP/Fiocruz)
- PhD dissertation: Interconnections between local production and access to medicines in the context of WTO TRIPS Agreement (2015)
- Project: Effects of health industrial and technological policies in the local production and supply to the Public Health System
  - Public grant by Ministry of Health/CNPq (2014-2017) “National network for health policy research: knowledge for the fullfilment of the universal right to health”
  - Coordination: Group of Economics of Inovation, Institute of Economy, Federal University of Rio de Janeiro
  - Institute of Studies on Collective Health, Federal University of Rio de Janeiro



Challenges to implement and develop the Health Industrial Complex (2016)



Vulnerabilities of the Health Industrial Complex (2018)

Public Production of medicines in Brazil: technological capacity and access (2018)

Context

- Brazil is not the country of origin of transnational pharmaceutical companies
- Brazil is not a major player in exportation of health technologies to global health donnors

BUT

- Brazil is a big country (continental dimension and population)
- Classified as a pharmerging country (rapid growth in sales)
- 7th position of the world pharmaceutical market (2018)

Population and Health system

Population (2021): 212.8 million
27 federative units: 26 states and Federal District
Three government levels: Federal, States, Municipalities

Public subsystem

- **Unified Health System (SUS) – funded by taxpayers, all citizens are entitled to use SUS, free of charge at the point-of-care. 71% of the Brazilian population relies exclusively on SUS (2013)**
- for civil servants (civil and military)

Private subsystem

- voluntary health insurance often funded by individuals, families, and/or employers
- out-of-pocket direct payment for health services

Final consumption (expenditure) of medicines by families and the government, 2010-2017

	BRL million for 2019			% of Total Final Consumption		
Year	**Families**	**Government**	**Total**	**Families**	**Government**	**Total**
2010	103,906	11,788	115,694	90	10	100
2011	103,707	11,455	115,162	90	10	100
2012	108,301	10,909	119,210	91	9	100
2013	110,814	11,876	122,690	90	10	100
2014	116,730	12,426	129,156	90	10	100
2015	111,911	13,166	125,076	89	11	100
2016	111,159	11,325	122,485	91	9	100
2017	111,265	9,079	120,344	92	8	100

Source: Vieira and Santos (2020). O setor farmacêutico no Brasil sob as lentes das contas-satélite em saúde. Free translation of the table

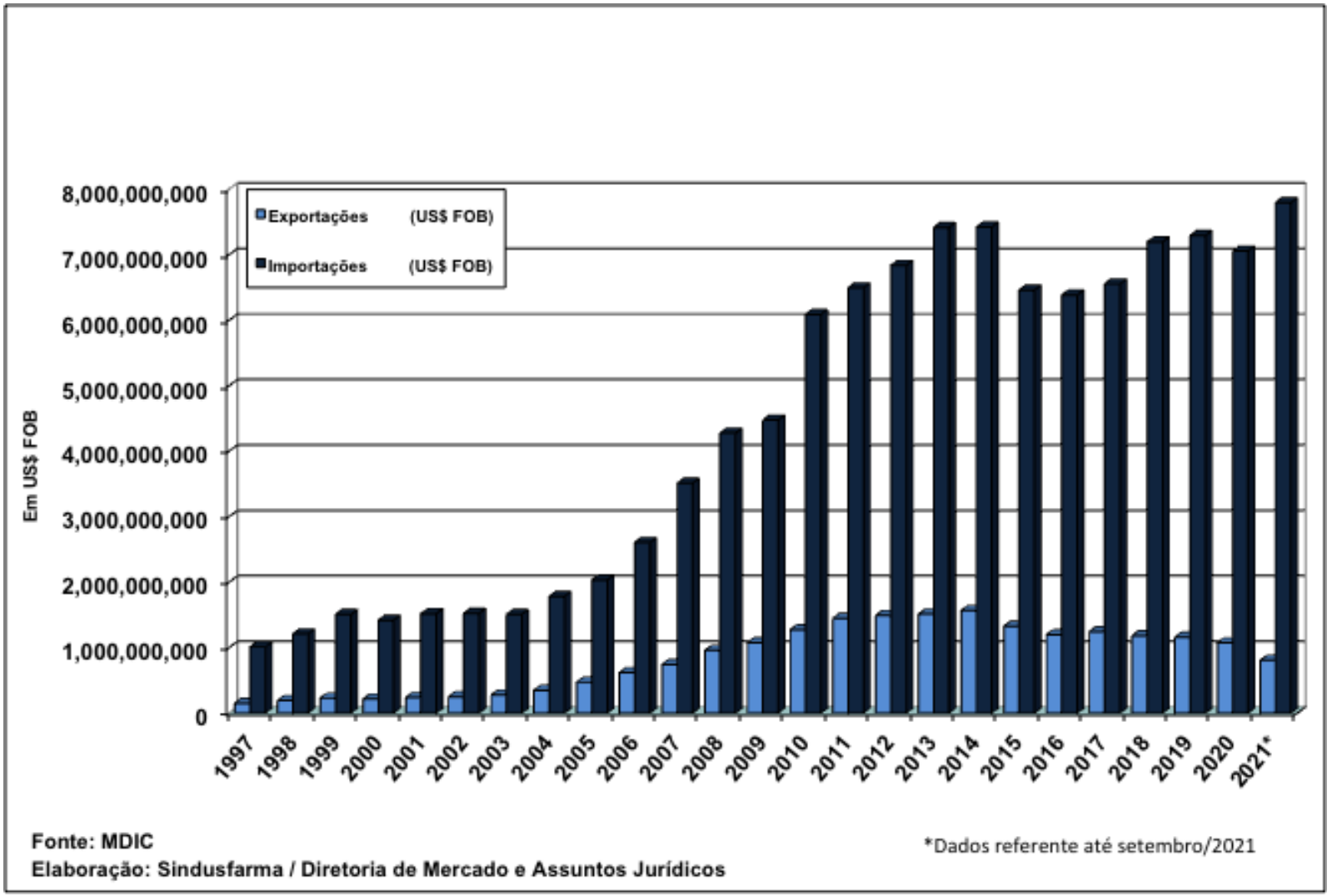
Pharmaceutical industry in Brazil

- Medicines (final product)
  - Transnational pharmaceutical companies (mostly imported medicines)
  - National pharmaceutical companies (generic and incremental innovation)
  - Public manufacturers

- Active pharmaceutical ingredient (API)
  - National and foreigner companies (112 manufacturing facilities)
  - Increase on importation US$ 571,7 millions to US$ 2 billions between 2003 and 2019 (average of 8.2% per year)

Source: Paranhos, J et al. (2021). Desenvolvimento da indústria farmoquímica no Brasil e na Argentina: diagnóstico, desafios e oportunidades. V ENEI

Brazilian trade balance for medicines (final product), 1997-Sep/2021

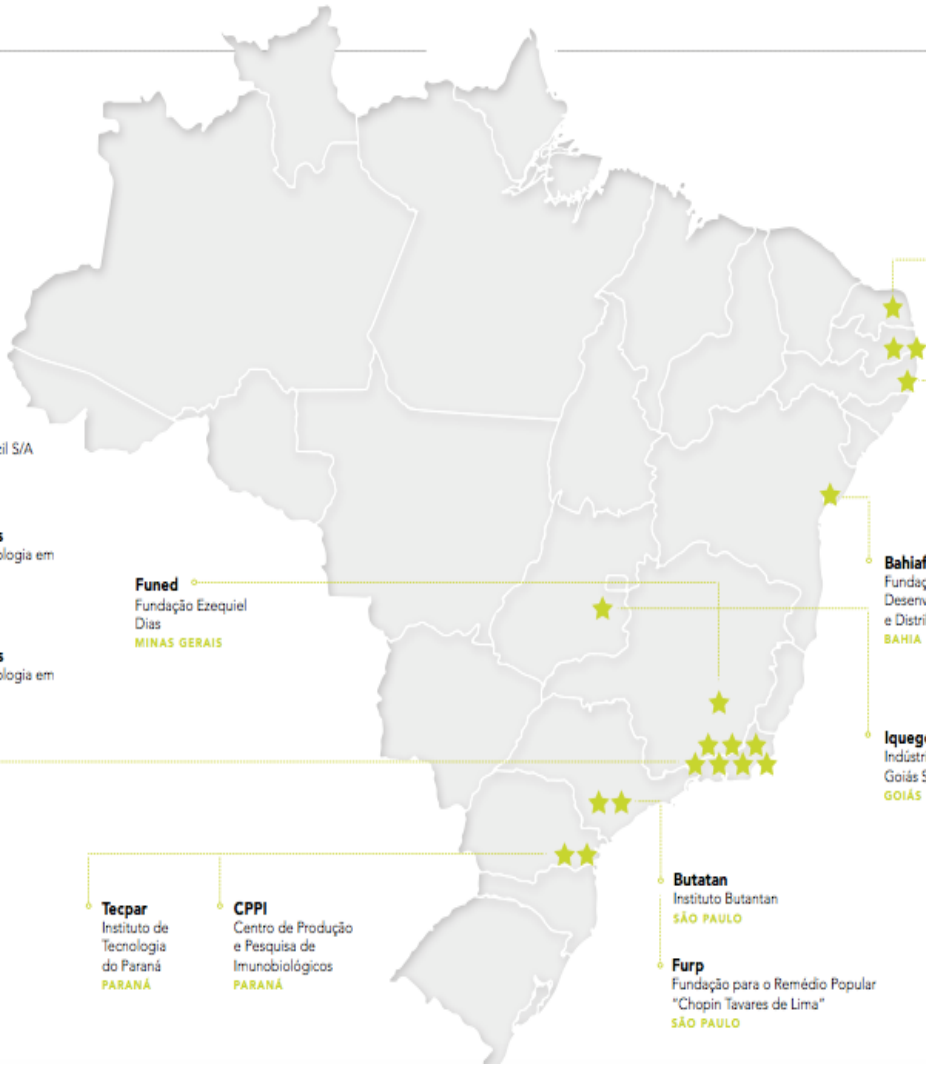


Source: SINDUSFARMA

Public manufacturers (ALFOB)

LABORATÓRIOS ASSOCIADOS

Atualmente, a ALFOB conta com 18 Laboratórios Farmacêuticos associados, e com representação formal junto ao Ministério da Saúde e ao grupo gestor do Complexo Industrial da Saúde. A maioria de seus associados está vinculada a governos estaduais, quatro são ligados a universidades e cinco a instituições federais (três pertencem às Forças Armadas: Marinha, Exército e Aeronáutica, e dois diretamente ao Ministério da Saúde).



IVB
Instituto Vital Brazil S/A
RIO DE JANEIRO

Biomanguinhos
Instituto de Tecnologia em Imunobiológicos
RIO DE JANEIRO

Farmanguinhos
Instituto de Tecnologia em Fármacos
RIO DE JANEIRO

Laqfa
Laboratório Químico-Farmacêutico da Aeronáutica
RIO DE JANEIRO

LFM
Laboratório Farmacêutico da Marinha
RIO DE JANEIRO

FAP
Fundação Ataulpho de Paiva
RIO DE JANEIRO

LQFex
Laboratório Químico e Farmacêutico do Exército
RIO DE JANEIRO

Funed
Fundação Ezequiel Dias
MINAS GERAIS

Tecpar
Instituto de Tecnologia do Paraná
PARANÁ

CPPI
Centro de Produção e Pesquisa de Imunobiológicos
PARANÁ

Butatan
Instituto Butantan
SÃO PAULO

Furp
Fundação para o Remédio Popular "Chopin Tavares de Lima"
SÃO PAULO

Nuplam/UFRN
Núcleo de Pesquisa em Alimentos e Medicamentos
RIO GRANDE DO NORTE

Lafepe
Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes S/A
PERNAMBUCO

Bahiafarma
Fundação Baiana de Pesquisa Científica e Desenvolvimento Tecnológico, Fornecimento e Distribuição de Medicamentos
BAHIA

Iquego
Indústria Química do Estado de Goiás S/A
GOIÁS

IPeFarM
Instituto de Pesquisa em Fármacos e Medicamentos
PARAÍBA

Certbio
Laboratório de Avaliação e Desenvolvimento de Biomateriais do Nordeste
PARAÍBA

RBPPM

Os Laboratórios Oficiais estão situados nas regiões Nordeste, Centro-Oeste, Sudeste e Sul e compõem a Rede Brasileira de Produção Pública de Medicamentos (RBPPM). A capacidade instalada existente na RBPPM apresenta um potencial de 16,6 bilhões de Unidades Farmacêuticas/ano.

Alfob (Association of Official Pharmaceutical Manufacturers of Brazil) /Federal Council of Pharmacy, 2019.

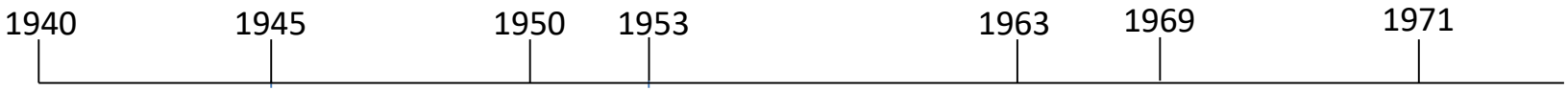
Potential to produce 16.6 billion pharmaceutical units/year

To discuss the connections between health policies and government strategies to stimulate local production of medicines in Brazil

Categories:

- Coordination
- Priority needs
- Demand/financing
- Target (API, medicine/final product, key-intermediates)

Exclusion of patent protection for pharmaceuticals



Incentives to bring foreign companies to manufature at the national territory

Exclusion **pharmaceutical products** from patent protection

Creation of the Ministry of Health (Service of Profilatic Products → procurement of sera and vaccines

Decree 52,471

Constitution of a group involving several Ministeries (Geifar); coordinated by the Ministry of Health

Guidelines

- Incentives to import and locally produce API
- Diagnostic of public manufacturers needs
- Ceiling prices for medicines
- Review of industrial property law to allow national production
- R&D

Decree 52,471

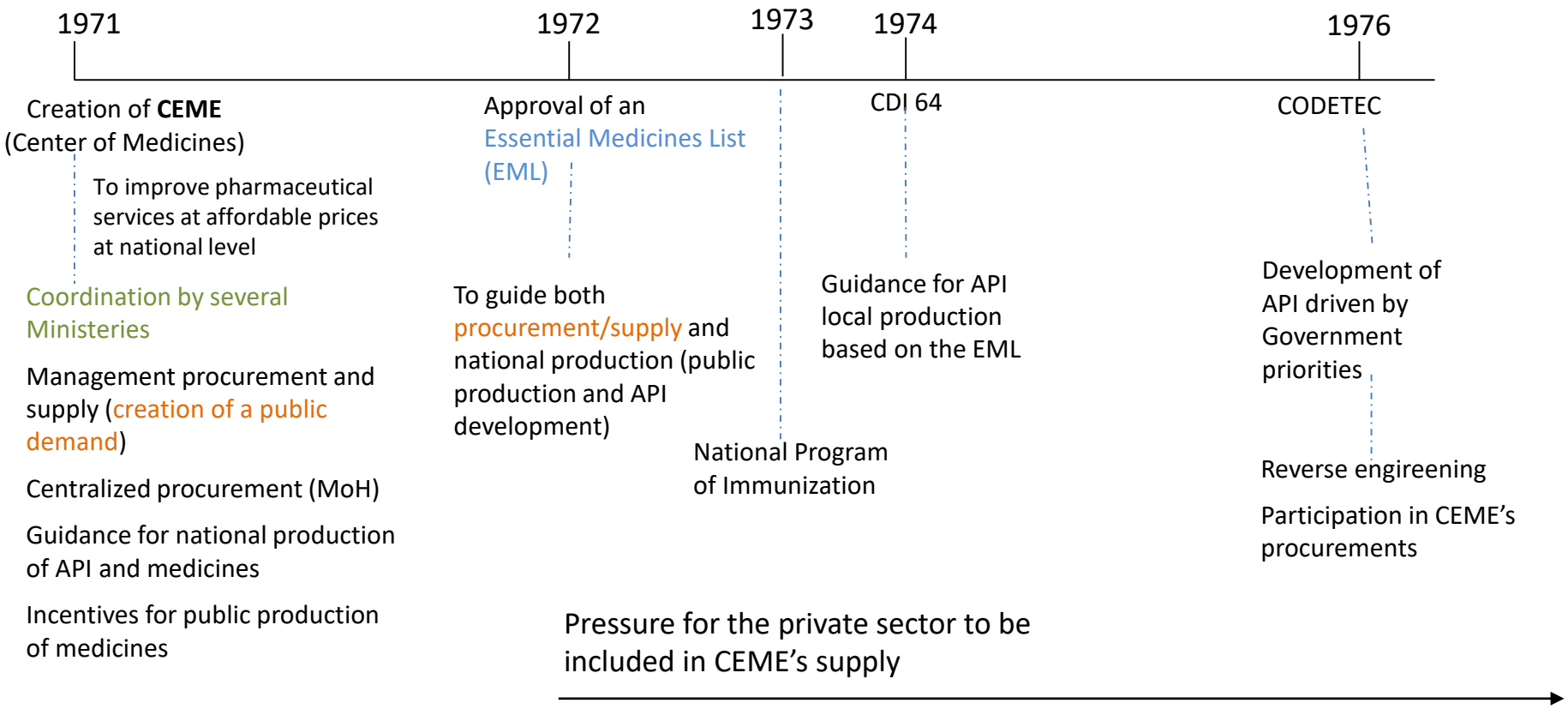
Priority and basic list of biological products and inputs for pharmaceutal use in humans and veterinary (to meet health needs and guide national production)

Law 5,772

Exclusion **pharmaceutical process** from patent protection

Source: Based on literature review and analysis of oficial documents and legislation

Connecting centralized demand with production



Source: Based on literature review and analysis of oficial documents and legislation

Laboratório	UF	Ano de fundação
Laboratório de Tecnologia Farmacêutica (LTF), Universidade Federal da Paraíba	Paraíba	–
Faculdade de Farmácia, Odontologia e Enfermagem (FFOE), Universidade Federal do Ceará	Ceará	–
Laboratório Químico Farmacêutico do Exército (LQFE), Ministério do Exército	Rio de Janeiro	1808
Laboratório Farmacêutico da Marinha (LFM), Ministério da Marinha	Rio de Janeiro	1906
Fundação Ezequiel Dias (FUNED), Secretaria de Estado de Saúde	Minas Gerais	1907
Instituto Vital Brazil S.A. (IVB), Secretaria de Estado de Saúde	Rio de Janeiro	1918
Instituto de Tecnologia de Fármacos (FAR-MANGUINHOS), Fundação Oswaldo Cruz	Rio de Janeiro	1956
Indústria Química do Estado de Goiás (IQUEGO), Secretaria de Estado de Saúde	Goiás	1964
Laboratório Farmacêutico do Estado de Pernambuco S.A. (LAFEPE), Secretaria de Estado de Saúde	Pernambuco	1967
Laboratório de Ensino, Pesquisa e Extensão em Medicamentos e Cosméticos (LEPMC), Universidade Estadual de Maringá	Paraná	1967
Laboratório Farmacêutico de Santa Catarina (LAFESC), Secretaria de Estado de Saúde	Santa Catarina	1969
Laboratório Químico Farmacêutico da Aeronáutica (LAQFA), Ministério da Aeronáutica	Rio de Janeiro	1971
Fundação para o Remédio Popular (FURP), Secretaria de Estado de Saúde	São Paulo	1972
Laboratório Farmacêutico do Rio Grande do Sul (LAFERGS), Fundação Estadual de Produção e Pesquisa em Saúde	Rio Grande do Sul	1972
Laboratório Industrial Farmacêutico de Alagoas (LIFAL), Secretaria de Estado de Saúde	Alagoas	1974
Laboratório de Produção de Medicamentos (LPM), Universidade Estadual de Londrina	Paraná	1989
Núcleo de Pesquisa em Alimentos e Medicamentos (NUPLAN), Universidade Federal do Rio Grande do Norte	Rio Grande do Norte	1991
Laboratório Industrial Farmacêutico do Estado da Paraíba (LIFESA), Secretaria de Estado de Saúde	Paraíba	1997
Total		

Year of creation

8 public manufacturers created between 1964-1974

Source: Oliveira, E. A. D., Labra, M. E., & Bermudez, J. (2006). A produção pública de medicamentos no Brasil: uma visão geral. Cadernos de Saúde Pública, 22, 2379-2389.

Evolution of CEME's expenditure (Cr$) with medicines procurement and supply and modernization of public manufacturers, 1972-1977

Year	Medicines Procurement and Supply	Modernization of public manufacturers	Research
1972	35,244	-	-
1973	69,214	-	3,274
1974	190,856	5,038	10,537
1975	287,951	3,059	14,636
1976	355,191	10,623	10,457
1977	719,000	9,918	7,001

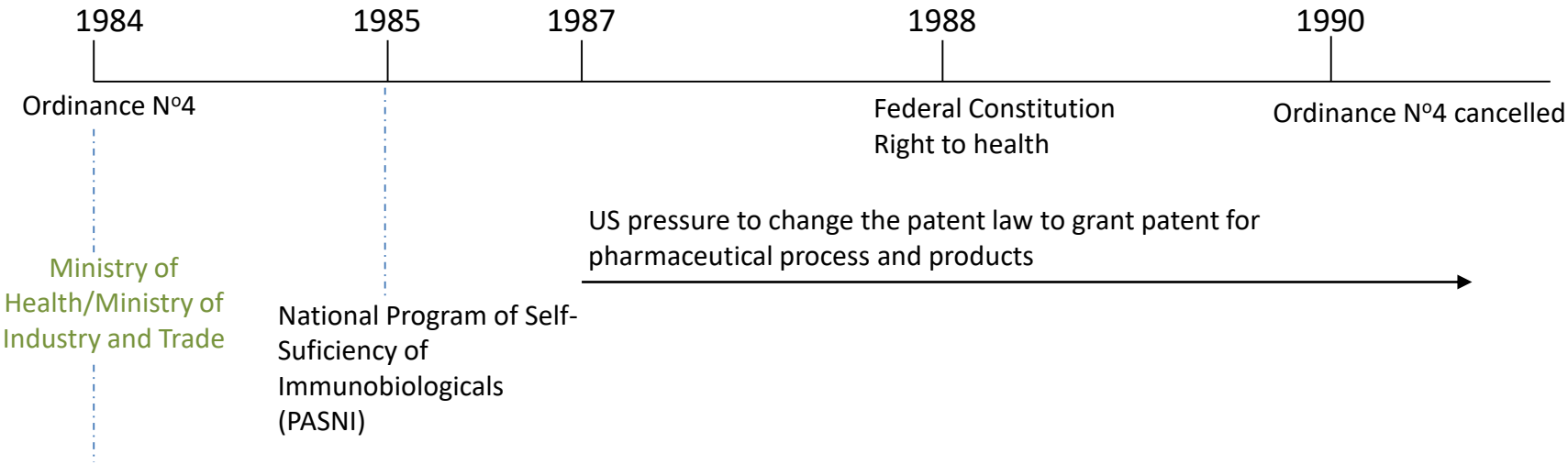
Source: Cordeiro, 1980

Participation of different industrial segment at CEME's procurement and production

Year	1972	1973	1976	1977
Participation				
Public Manufacturers	73.60%	66.30%	21%	45%
Private Industry	26.40%	25.20%	76%	53%
Importation		8.50%	3%	2%

Source: Marquesini & Carmo (1980)

Efforts for API national production



National production of API, 1982-1987

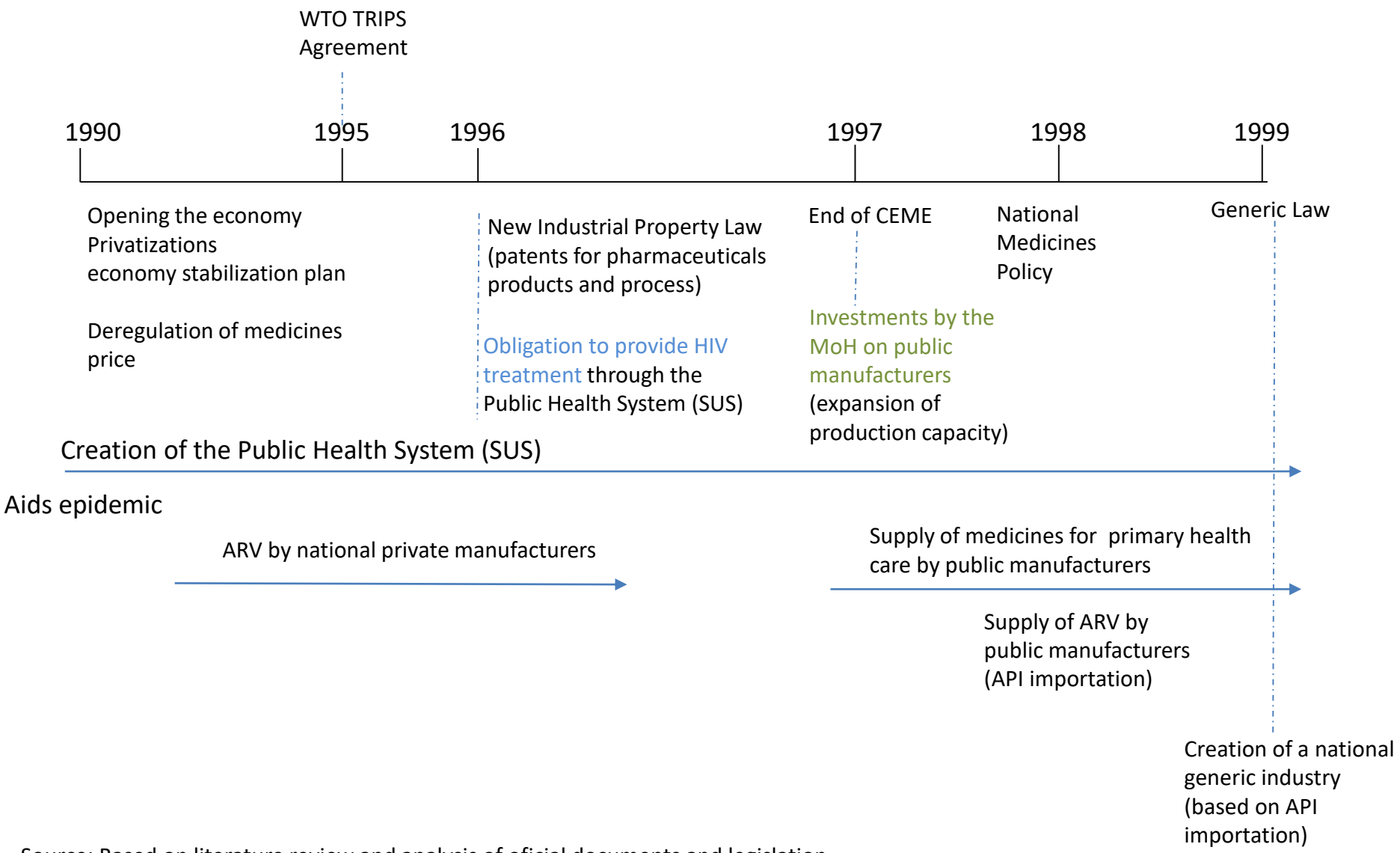
Year	US$ million
1982	268
1983	259
1984	297
1985	321
1986	417
1987	521

Estimates of 60-70% of the national market

Source: Queiroz & González (2001)

Source: Based on literature review and analysis of oficial documents and legislation

The decade of contradictions



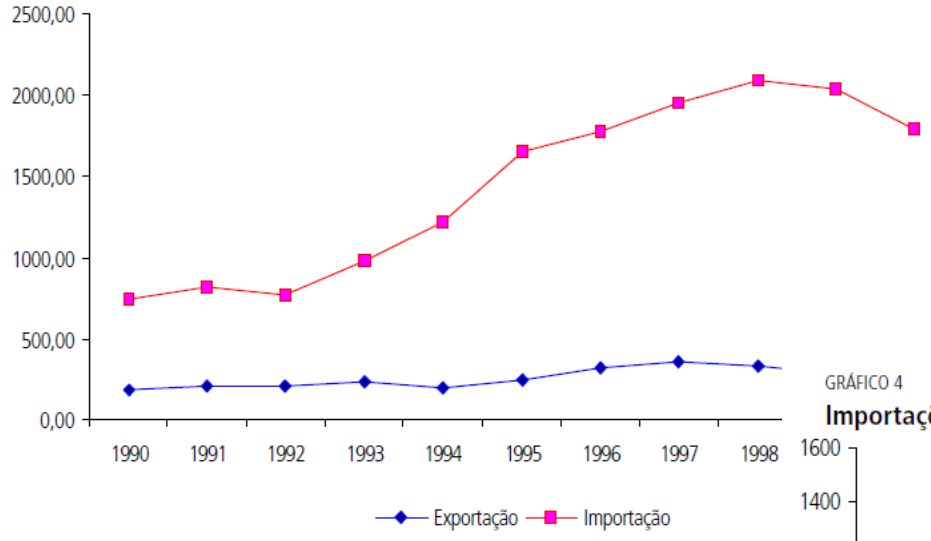
Source: Based on literature review and analysis of oficial documents and legislation

Changes in the API and medicines market

Exportation and importation of **API** in Brazil, 1990-2000

Exportação e importação de fármacos no Brasil: delimitação ampla (capítulos 28 e 29 da Secex)[1]

(Em milhões de US$ FOB)



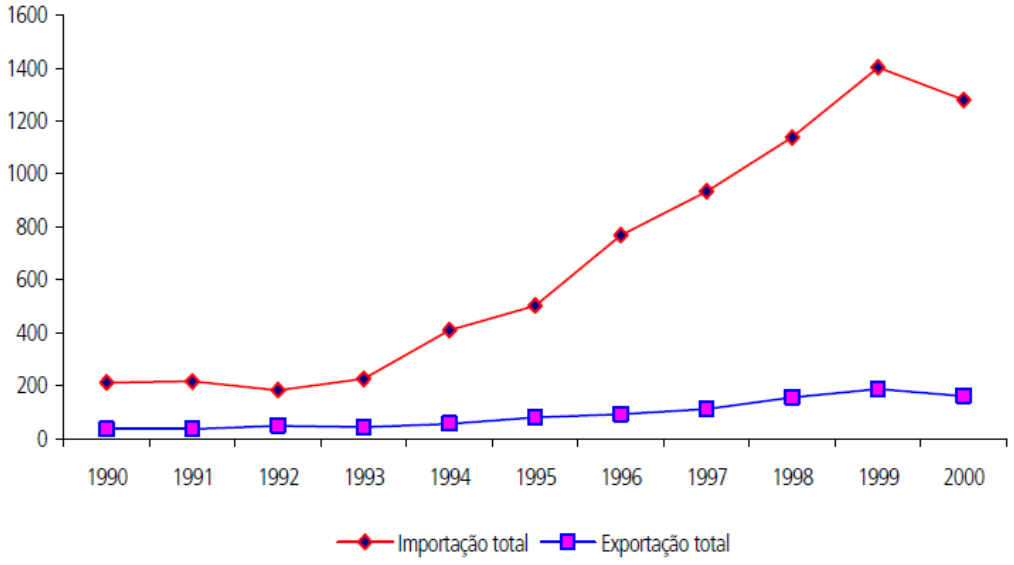
Fonte: Secex e Pereira (1999). Elaboração dos autores.

Nota: [1]É importante relembrar que há dificuldades em adequar as NCMs às NBMs, ou seja, as compa
portação e exportação de 1990 a 1996 e a de 1997 a 2000 devem ser feitas levando em consic

Exportation and importation of **Medicines (final product)** in Brazil, 1990-2000

GRÁFICO 4

Importações e exportações de medicamentos

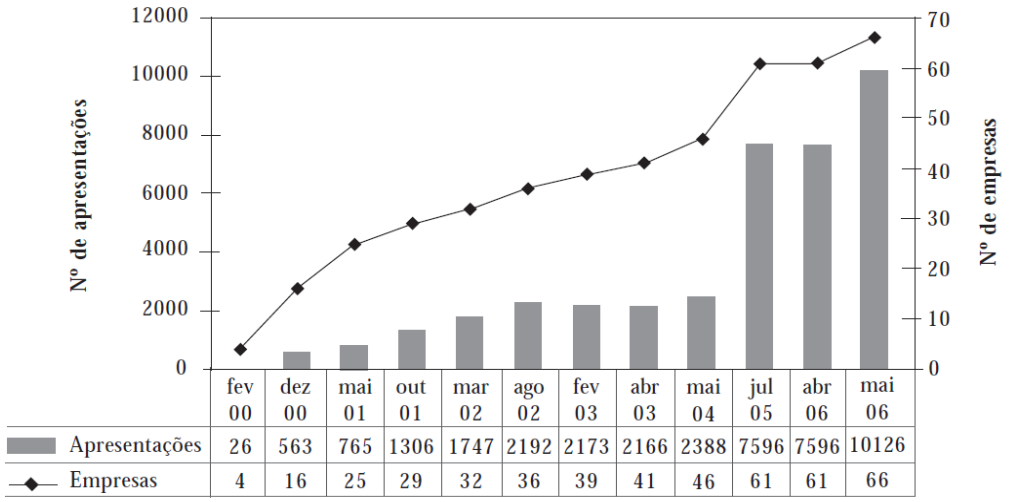


Fonte: Secex. Elaboração dos autores.

Source: Magalhães et al. (2003). Evolution, trends and characteristics of importation and exportation of API and medicines: analysis of the foreign trade balance of Brazilian pharmaceutical industry. Brasília:IPEA.

Changes in the generic market

Evolution of the generic market (Feb/2000-May/2006): companies x pharmaceutical dosage forms



	fev 00	dez 00	mai 01	out 01	mar 02	ago 02	fev 03	abr 03	mai 04	jul 05	abr 06	mai 06
Apresentações	26	563	765	1306	1747	2192	2173	2166	2388	7596	7596	10126
Empresas	4	16	25	29	32	36	39	41	46	61	61	66

Apresentações = pharmaceutical dosage forms

Empresas = Companies

Source: Quental et al (2008). Generic drugs in Brazil, impacts of public policies upon national industry. Ciência e Saúde Coletiva, 13 (Sup)

Companies's market share of generic medicines (Sales: aug/2002-Aug/2005)

	Empresas	Participação (%)			
		ago/02	ago/03	ago/04	ago/05
1	Medley	27,46	26,44	27,65	29,13
2	EMS Sigma Pharma	18,05	19,91	21,64	25,91
3	Biosintética	17,92	13,00	12,44	12,42
4	Eurofarma	11,12	9,99	10,17	9,05
5	Ranbaxy	10,30	8,80	7,20	5,13
6	Novartis	4,31	4,70	4,75	3,97
7	Merck	2,74	3,56	3,35	2,82
8	Hexal do Brasil	1,58	1,74	2,17	1,92
9	Germed	0,17	0,28	0,26	1,78
10	Mepha	0,07	0,49	1,27	1,30
	Total	93,00	88,91	91,20	93,43

Trying again

PITCE
Industrial, Technological and Foreign Trade Policy

Inclusion of pharmaceutical industry as strategic área (API and medicines)

Biotechnology and nanotechnology

Descentralization of pharmaceutical services for primary health care →

Challenges for public manufacturers to compete in public procurements at the subnational levels

Ministry of Health takes the lead on the industrial policy for medicines (Health Industrial Complex)

Compulsory license of efavirenz

Importation of generic version

Local production: API (national companies) and final product (public manufacturer)

Policy for Productive Development

Plan Brazil Bigger

PDP (Partnerships for Productive Development)

Priority list of medicines (SUS)

Technology transfer (TT) from the private to the public manufacturer

API produced at the national territory

Exclusivity on the public market during the TT

Expectation of price reduction

Source: Based on literature review and analysis of oficial documents and legislation

Technology transfer through PDP

- Challenges
  - Priority list
  - Evidence on price reduction for most of the cases, but concerns of those results in comparison with a competitive environment
  - Timeframe for technology transfer (up to 10 years) and risk of technology substitution in Therapeutic Guidelines
  - To increase technological capacity of public manufacturers (need also investments on R&D and education to allow technology accumulation)
- Opportunities
  - Follow-up on regulatory aspects over the TT
  - Inclusion of biological products (ongoing)

Source: Based on case studies and other analysis in the literature and official documents

Challenges for public manufacturers

- Coordination among the manufacturers and with the Ministry of Health
- Stability of public demand
- Focus on the national demand; few examples of exportation
- Approaches to address changes in therapeutic guidelines within technology transfer through PDP
- Portfolio update
- Financing to improve the productive site
- Investments in innovation
- Technological capacity and accumulation

Source: Chaves, GC; Azeredo, TB; Vasconcelos, DMM; Mendoza-Ruiz, A; Scopel, C; Oliveira, MA; Hasenclever, L (2018). Produção pública de medicamentos no Brasil: capacitação tecnológica e acesso. Rio de Janeiro:E-papers.

Contribution of public production to public health needs

1 – To address insufficient supply or descontinuation of production

Beggining of XX century – The creation of Federal Serum Therapy Institute of the Oswaldo Cruz Institute/RJ (1900) and Butantan Institute/SP (1901) is within a context of an epidemic of bubonic plague (1899) in Santos Port and challenges to quickly import the anti-plague serum from the sole producer Pasteur Institute (France).

1976 - Creation of the Immunobiologicals Technology Institute (Biomanguinhos) due to the external dependence of the *Neisseria meningitidis* vaccine (A and C) not being sufficient for the growing internal demand. Technology was transferred to Biomanguinhos. 80 million doses supplied to the population

Beggining of 2000's – production of benznidazol for Chagas disease was about to be descontitnued by the originator multinational company and Lafepe received the technology transfer, being the single-supplier for years. API also produced by a national pharmaceutical company.

Source: Based on literature review

2 - Serums for venomous animals

- Public production covers 100% of the supply to the Public Health System (ALFOB,2019)

- Four public manufacturers:
  - Vital Brazil Institute/RJ
  - Butantan Institute/SP
  - Foundation Ezequiel Dias/MG
  - Center for Research and Production of Immunobiologicals (Centro de Pesquisa e Produção de Imunobiológicos - CPPI)/PR

Alfob (Association of Official Pharmaceutical Manufacturers of Brazil) /Federal Council of Pharmacy, 2019.

3 – Price regulation of monopoly medicines

ARVs adopted by SUS: patented or with pending patent applications (exclusive supplier in Brazil)

Strategy:

- **Estimates of production costs to support price negotiations** between the MoH and originator companies: Farmanguinhos / Fiocruz provided reference price for negotiations in 1999, 2001 and 2005 (Nelfinavir, Efavirenz, Lopinavir/ritonavir)

- **Supply** when a compulsory license is issued (efavirenz, 2007)

Examining the production costs of antiretroviral drugs

Eloan Pinheiro[a], Ashwin Vasan[b], Jim Yong Kim[b,c], Evan Lee[d], Jean Marc Guimier[d] and Joseph Perriens[a]

From the [a]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland, the [b]Partners In Health, Boston, the [c]Department of Social Medicine, Harvard Medical School, Boston, Massachusetts, USA, and the [d]Management Sciences for Health – Europe, Ferney Voltaire, France.

AIDS 2006, **20**:1745–1752

4 – Addressing patent barrier

Farmanguinhos/Fiocruz filed three pre-grant oppositions (third party observation):

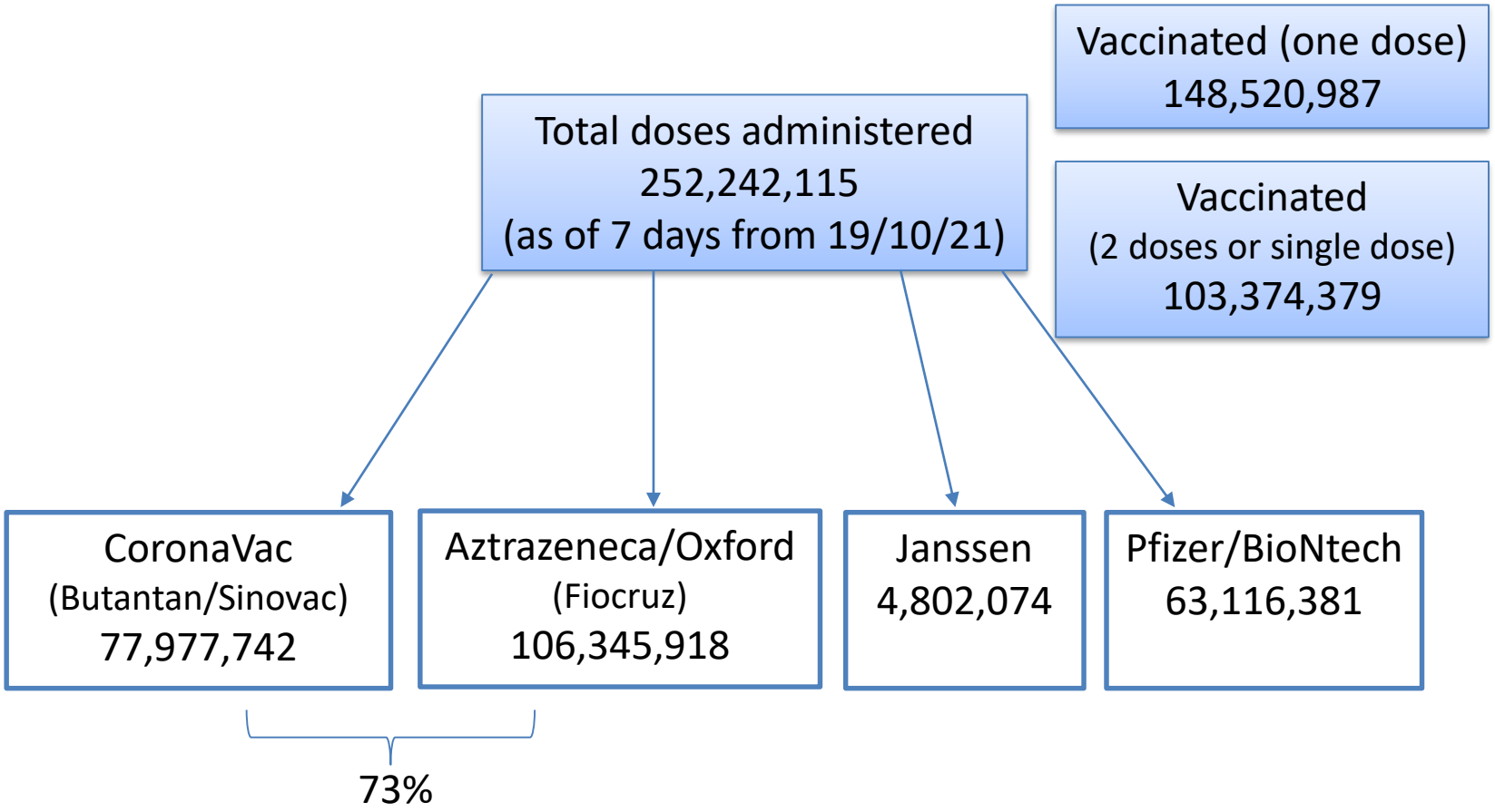
- 2005 – Patent application for Lopinavir/ritonavir
- 2006 – Patent application for Tenofovir
- 2017 – patent application for Sofosbuvir

5 – Development of formulations for NTD

- Farmanguinhos/Fiocruz and DNDi: development of fixed-dose combination of artesunate+mefloquine (ASMQ FDC) for malaria

- Lafepe and DNDi: pediatric dosage form (12.5mg) of benznidazol

6 – Supply and Production of two Covid-19 vaccines



Source: Ministry of Health (2021). Available at https://qsprod.saude.gov.br/extensions/demas_c19vacina/demas_c19vacina.html

6 - Supply through agreement for local production (Covid-19 vaccines)

- **Sinovac/Butantan**:
  - June/2020: agreement between Sinovac and Butantan (including funding from SP gov)
  - Co-development
  - Selection based on the possibility to absorb the technology
  - July/2020: Clinical trials phase III started in Brazil

- **Supply to SUS**
  - 17 January 2021: first vaccination in Sao Paulo
  - 19 January 2021: 6 millions doses supplied by MoH to 27 federative units

Sources:
DiarioOnline (2021). Ministério da Saúde conclui distribuição do 1º lote da CoronaVac.
South Centre (2021). Webinar on Manufacturing capacity of Covid-19 vaccines.
CNN Brasil (2021). Butantan entrega mais 2,2 milhões de doses da CoronaVac ao Ministério da Saúde

6 - Supply through agreement for local production (Covid-19 vaccines)

Biomanguinhos/Fiocruz: Technological prospecting of vaccines candidates

Anvisa's authorization to start clinical trials Oxford/Astrazeneca

Oxford/Astrazeneca-Fiocruz : MoU in July 2020, Technological Order (Etec) contract signed Sep/2020 (Phase I)

Supply to SUS (delivered)

- January: 2 million imported from India
- February: 2 million imported from India
- March/April: 21. 4 million (domestic production with imported API)
- May: 20.9 million (domestic production with imported API)
- June: 18.1 million (domestic production with imported API)
- July: 14.5 million (domestic production with imported API)
- August: 11.5 million (domestic production with imported API)

Phase II (June/2021): Technology transfer agreement signed between Fiocruz and Oxford-Astrazeneca

- Fiocruz receives cell and virus banks for the national production of the API

Source: Fiocruz (2021). "Fiocruz assina contrato de Transferência de Tecnologia da vacina Covid-19"; "Vacina Covid-19: Fiocruz recebe bancos de células e de vírus para produzir IFA nacional"

Final remarks

- Approaches to stimulate local production of medicines included: exclusion of patent protection for pharmaceutical products and processes; coordination by the health sector; establishing a list of priority medicines; ensuring a public demand
- However, local production of medicines
  - is vulnerable to external context and to internal political changes of priorities
  - Require long-term planning and investments
- Brazil's experience shows the consequences of TRIPS Agreement in pharmaceutical market and high prices of medicines
- Brazil continues to be highly dependent on the importation of API and medicines, bringing continuous challenges to respond to health needs within SUS
- Technology transfer poses challenges in terms of technological capacity of local producers
- Despite those challenges, throughout this period, Brazil has shown that having some productive capacity in place, specially from public manufacturers, has allowed the government to use them as part of the response to some of the health problems in the country