CEPI

CEPI RNA VACCINE REGULATORY WORKSHOP

RNA Workshop Presentation Slides

Day 2

Session 2 · Regulatory Basis in Practice

28–29 July 2026

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Presentation Slides — Day 2

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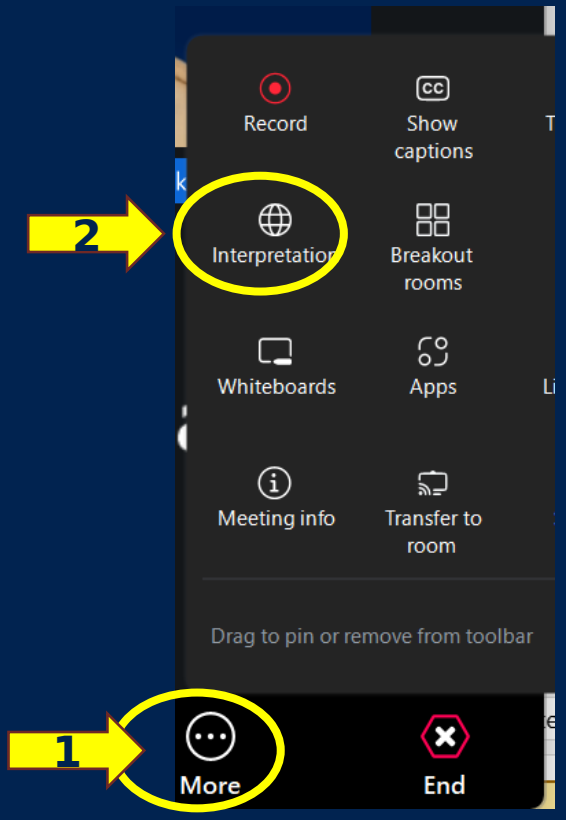
Regulatory Pathways in the Development of RNA Vaccines

28-29 July 2026

Instructions for Using Simultaneous Translation



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SESSION 2 · MODULE 1 · 10 MINUTES

Opening & Recap of Session 1

A CEPI-led workshop for NRA regulators of the Americas

CEPI

What Day 2 covers

Four modules build the answer to today's framing question — starting with this recap, then moving into emergency development, reliance, and inspection.

1	**Opening & Recap**	Recap of Session 1 and the framing question that runs through today.	YOU ARE HERE
2	**Development under emergency**	How development and review compress when time is short.	
3	**Reliance in the Americas**	Regional experience using others' decisions to move faster.	
4	**Product-specific GMP inspection**	Inspecting RNA and LNP manufacture against the right expectations.	

RECAP

What we established in Session 1

1 **The molecule**
mRNA elements — 5′ cap, UTRs, antigen ORF, poly(A) tail — each annotated and justified.

2 **The manufacture**
Cell-free IVT and LNP formulation; sequence-agnostic and faster to adapt.

3 **The RNA family**
Standard mRNA, self-amplifying RNA, and circular RNA — one diversifying platform.

4 **The platform question**
RNA, LNP, or both — the boundary shapes data-sharing and change management.

5 **Readiness & roles**
Six-domain self-assessment, product classification, and the two NRA roles.

What mRNA is — and what it does in the body

mRNA is a short-lived instruction, not a drug that lingers. The vaccine delivers the message; your own cells make the antigen.

1

Deliver

The lipid nanoparticle carries the mRNA into the cytoplasm of your cells — it stays outside the nucleus.

2

Translate

Ribosomes read the mRNA and build the target antigen, exactly as they read the cell's own messages.

3

Display

The antigen is shown to the immune system, which learns to recognise it. No live virus is involved.

4

Clear

The mRNA is broken down within days. It does not enter the genome and does not change your DNA.

Never enters the nucleus · **Never alters DNA** · **Cleared within days**

Why this makes a fast, adaptable platform

The same mechanism that keeps mRNA transient also makes it a versatile platform — the process barely changes when the target does.

Plug-and-play

Swap the coding sequence, keep the process. A new antigen does not mean a new manufacturing method.

Sequence-agnostic

No cell culture and no eggs. The same cell-free chemistry makes any construct, so scale-up is faster.

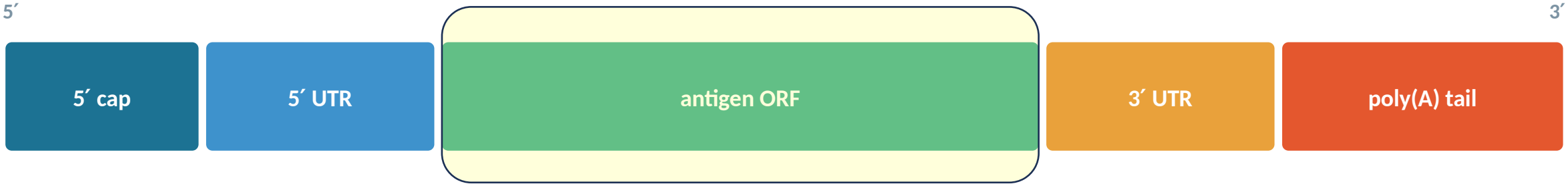
Transient & non-integrating

Expression is temporary and the genome is untouched, giving a well-characterised safety profile.

For an NRA: platform knowledge carries across products — the review of the process can be largely reused when only the sequence changes.

Anatomy of the mRNA construct

Read 5′ to 3′, every element is deliberate. Only the coding region changes from one product to the next.



5′ cap

Lets the ribosome recognize the message and shields it from rapid degradation.

5′ UTR

Tunes how efficiently the message is translated into protein.

antigen ORF

The coding region — the only part that changes between products.

3′ UTR

Stabilises the message and helps sustain expression.

poly(A) tail

A length-controlled tail that further stabilizes and boosts translation.

PLATFORM VARIABLE

Cell-free synthesis, then formulation

The mRNA is made in a tank with no living cells, then wrapped for delivery. The chemistry does not change when the sequence does.

1

DNA template

A linearised plasmid encodes the construct to be transcribed.

2

In-vitro transcription

Enzymes synthesise the mRNA — a cell-free reaction, no cell culture.

3

Purification

Template, enzymes, and reaction by-products are removed.

4

LNP encapsulation

The mRNA is wrapped in a lipid nanoparticle for delivery and stability.

5

Fill & finish

Formulate, fill, and release the finished product.

Sequence-agnostic and faster to adapt — the same platform process makes any construct.

One platform, three RNA formats

The molecule can take several forms. The differences change dose and durability — but the regulatory questions rhyme across all three.

Established

Standard mRNA

Encodes the antigen directly. The most mature format and the basis of the first licensed products.

saRNA

Self-amplifying RNA

Carries a replicase, so each molecule makes more copies inside the cell — potentially much lower doses.

circRNA

Circular RNA

A closed loop with no free ends, aiming for greater stability and longer-lasting expression.

Different molecules, one diversifying platform — the review builds on shared foundations.

Where do you draw the ‘platform’ line?

‘Platform’ can mean the RNA, the delivery system, or both together. The boundary is a regulatory choice with real consequences.

A

RNA only

The message is the platform; the LNP is assessed per product.

B

LNP only

The delivery system is the platform; each new RNA rides on it.

C

RNA + LNP together

The whole system is treated as a single platform.

Why it matters: the boundary you choose shapes what data can be shared across products and how post-approval changes are managed.

Assessing readiness, and knowing your role

A self-assessment across six regulatory domains, a product classification, and the two roles an NRA can play — the set-up for Session 2.

Six-domain self-assessment

1. Scientific expertise
2. Analytical infrastructure
3. Legal & regulatory authority
4. Operational systems
5. Collaboration mechanisms
6. RNA GMP inspection readiness

Product classification — vaccine, biological, or gene therapy? The category sets the pathway, dossier, and inspectorate.

A

Manufacturing-country NRA

Oversees development and production at source — the full dossier, GMP, and release.

B

Importing-country NRA

Relies on the work of others where possible, focusing effort on local decisions.

Immunoscript™
LIFE SCIENCE

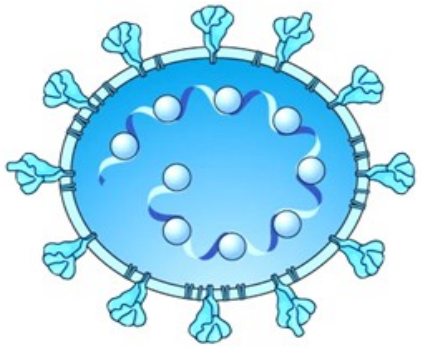
The mRNA Vaccine Revolution

Core principles, safety, and regulatory pathways of platform technologies

PLATFORM SCIENCE | CLINICAL SAFETY | REGULATORY PATHWAYS

Four Generations of Vaccine Technology

Vaccine 1.0



Whole-organism either live and weakened, or killed forms

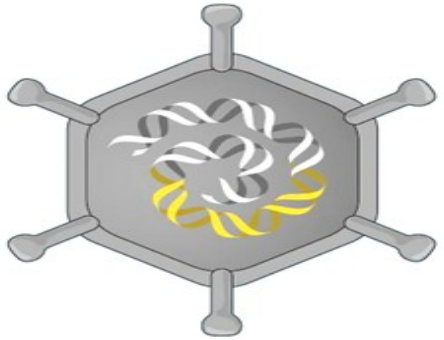
- Polio, hepatitis A, rabies, influenza, yellow fever, measles, mumps, rubella, typhoid

Vaccine 2.0

Recombinant subunit vaccines, consisting of specific protein antigens or protein components

- Seasonal influenza, hepatitis B, HPV

Vaccine 3.0



Adenoviral non replicating DNA and plasmid DNA

- VSV-Ebola vaccine
- COVID19

Vaccine 4.0

Synthetic in nature, carries the cells' message to make the antigen for a particular infection

- COVID19

Process Economics

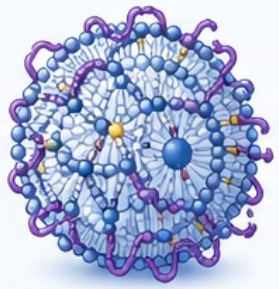
Time to manufacture

mRNA-LNP VACCINES: MECHANISMS OF ACTION AND PATHWAYS TO NEXT-GENERATION IMMUNITY

Powerful, Coordinated Immunity, Millions of Lives Saved. Continued Innovation for a Healthier Future.

Nucleoside-modified mRNA-lipid-nanoparticle (mRNA-LNP) vaccines confer a high level of protection against severe COVID-19 and, since their first authorization for human use in 2020, have saved millions of lives. Their efficacy relies ort the induction of powerful and coordinated innate and adaptive immune responses.

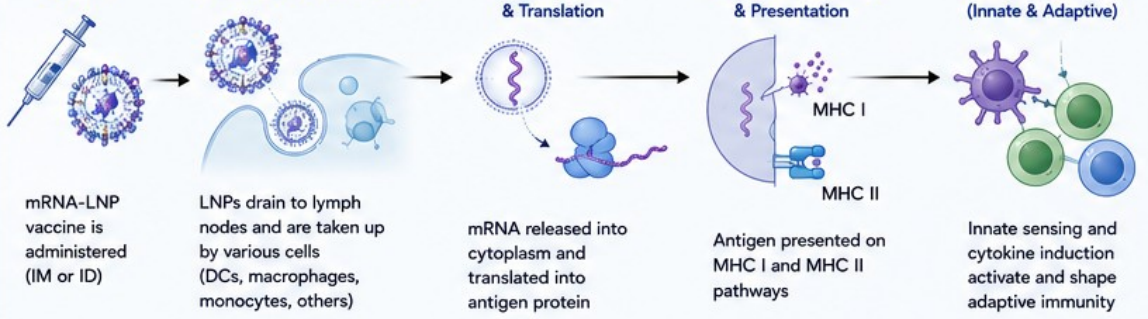
THE mRNA-LNP VACCINE PLATFORM



- Nucleoside-modified mRNA (wrapped on surface)
- Ionizable lipid
- Phospholipid
- Cholesterol
- PEG-lipid

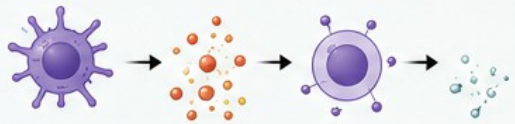
- Protects mRNA
- Enables efficient cellular delivery
- Provides intrinsic adjuvant activity
- Scalable and adaptable platform

MECHANISMS OF ACTION: FROM INJECTION TO IMMUNITY



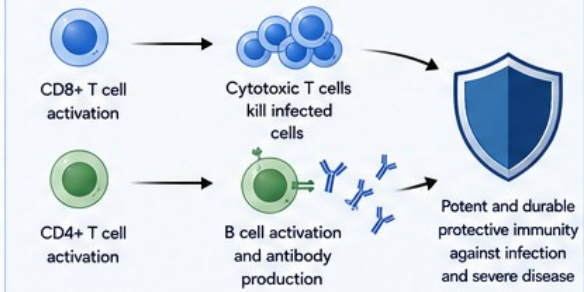
1. mRNA-LNP vaccine is administered (IM or ID)
2. LNPs drain to lymph nodes and are taken up by various cells (DCs, macrophages, monocytes, others)
3. mRNA released into cytoplasm and translated into antigen protein
4. Antigen presented on MHC I and MHC II pathways
5. Innate sensing and cytokine induction activate and shape adaptive immunity

INNATE IMMUNE RESPONSE



- Pattern recognition receptors (e.g., TLR3, TLR7/8, RIG-I, MDAS) sense mRNA/LNP components
- Induction of type I IFNs and pro-inflammatory cytokines
- Activation and maturation of dendritic cells and other myeloid cells
- Upregulation of co-stimulatory molecules and chemokines

ADAPTIVE IMMUNE RESPONSE



KEY KNOWLEDGE GAPS

- How are LNPs sensed by the immune system and how do they exert adjuvant activity?
- What are the specific signals and cellular pathways critical for protective immunity?
- Is it feasible to uncouple vaccine immunogenicity from reactogenicity?
- How do different components influence the quality, magnitude and durability of responses?

PLATFORM COMPONENTS THAT CAN BE MODIFIED

- mRNA sequence and structure (antigen, UTRs, modifications)
- Lipid composition and ratios (ionizable lipids, helper lipids, cholesterol, PEG-lipid)
- Particle size, charge and surface properties
- Dose and route of administration
- Formulation and storage conditions

ADVANCING NEXT-GENERATION mRNA VACCINES

Enhance Immunogenicity
Stronger, broader and more durable immunity (including mucosal and cellular responses)

Improve Tolerability
Reduce reactogenicity while maintaining or enhancing protective efficacy

Broaden Protection
Design for variant-resistant and pan-pathogen responses

Optimize Delivery
Refine LNPs and routes to target relevant cells and tissues

Expand Access
Scalable, stable and affordable vaccines for global health equity

Build Trust
Transparent science, pharmacovigilance and public engagement

THE IMPACT

Deepening our understanding of mRNA-LNP vaccine mechanisms will accelerate the development of next-generation vaccines to tackle emerging and challenging pathogens for which effective vaccines do not exist or need improvement.

mRNA-LNP vaccines represent a platform with extraordinary potential—driven by science, guided by immunology, and focused on saving lives today while preparing for the health challenges of tomorrow.

nature

NATURE
Nature, vol. 654, pp. 892–901 (2026)

The Regulatory Journey

01

Phased clinical trials

Strict progression through Phase I, II and III human testing before any licensure decision is taken.

02

Expedited transition

Emergency Use Authorisation bridged early rollout ahead of full Biologics License Application approval.

03

The platform advantage

Seasonal strain updates use a streamlined, flu-shot style variation pathway rather than a fresh dossier.

04

Continuous pharmacovigilance

Active post-market surveillance tracks real-world outcomes across every authorised population.

SO WHAT?

Because the platform itself is what gets licensed, a strain change is handled as a variation rather than a fresh dossier. That single regulatory fact is why mRNA can move at outbreak speed.

Clinical Safety & Metrics

01

Expected reactogenicity

Mild, temporary effects — fatigue, a sore arm, short-lived fever — consistent with a working immune response.

02

Modified nucleosides

Chemical modification of the mRNA minimises unintended innate inflammation without blunting immunogenicity.

03

Exceptional efficacy

Over 90% protection against the initial strains, with a sustained reduction in hospitalisation and ICU admission.

04

Rare event tracking

Low-risk, manageable instances of transient myocarditis identified early and mitigated through label and dosing guidance.

SO WHAT?

Reactogenicity is expected and self-limiting; the rare events are known, tracked and manageable. Regulators licensed the platform on exactly that distinction.

India's Regulatory Success Story

2022

DCGI emergency use authorisation

GEMCOVAC®-19 became the world's first thermostable mRNA COVID-19 vaccine to reach authorisation — and the first developed wholly outside the US or EU.

Sources: DCGI / CDSCO authorisation records; Gennova

GEMCOVAC®-19	India's first indigenously developed mRNA vaccine. DCGI emergency use authorisation, June 2022; GEMCOVAC®-OM, the Omicron-specific booster, followed in 2023.
Thermostability	Stable at 2–8 °C, enabling rural distribution without the ultra-cold chain that Pfizer and Moderna require.
Regulatory adaptation	DCGI mirrored global EUA frameworks while weighting local feasibility and manufacturing readiness.
Conditional approval	Granted against a commitment to ongoing pharmacovigilance and real-world safety data.
Strategic impact	Validated India's biotech ecosystem and set the precedent for oncology and infectious-disease mRNA therapies.

The Outlook

01

Expanding targets

Programmes now extend to rabies, influenza, Nipah and Ebola alongside COVID-19, at stages from preclinical through clinical development.

02

Active pipeline

Clinical trials underway in personalised oncology, where the platform's speed of iteration matters most.

03

Agile defence

New target sequences can be synthesised and scaled within days of a genome being published.

SO WHAT?

The asset is the speed of iteration, not any one target. Days from sequence to candidate means the target list keeps growing while the manufacturing platform stays unchanged.

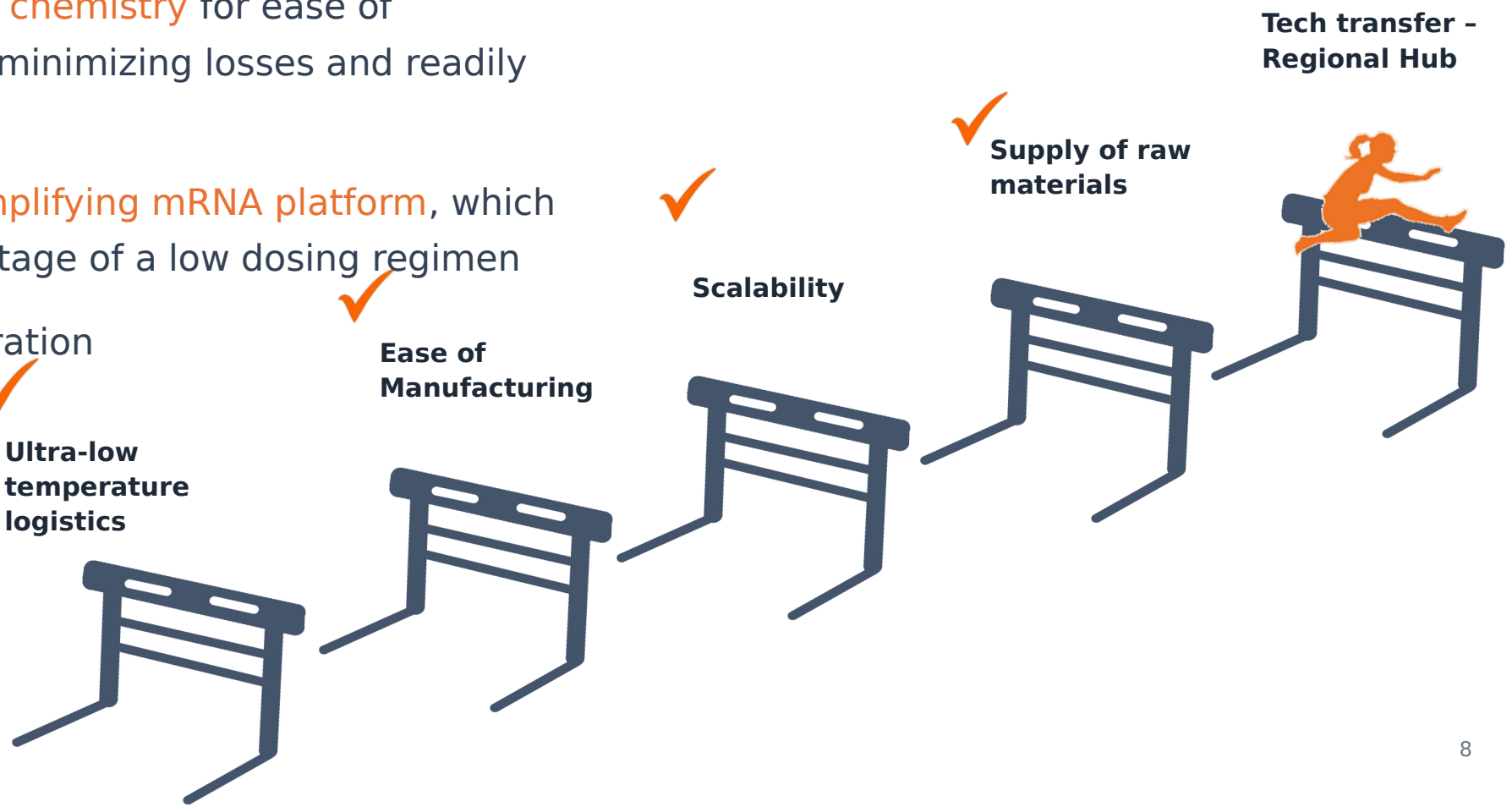
Pipeline stages as of July 2026. Rabies, influenza, Nipah and Ebola programmes are in development, not authorised.

Challenges in Democratising the Platform

Differentiating Technology

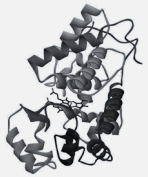
- Stable at 2 - 8 °C
- Uses adsorption chemistry for ease of manufacturing, minimizing losses and readily scalable
- Uses the self amplifying mRNA platform, which gives the advantage of a low dosing regimen
- Backward Integration

Overcoming Challenges

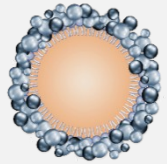


Disease Agnostic Platform

Cofactors, Nucleotides & Lipids



Enzyme

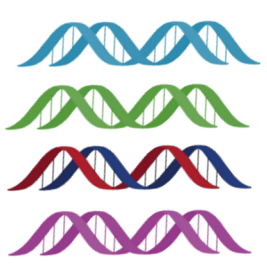


CLNE

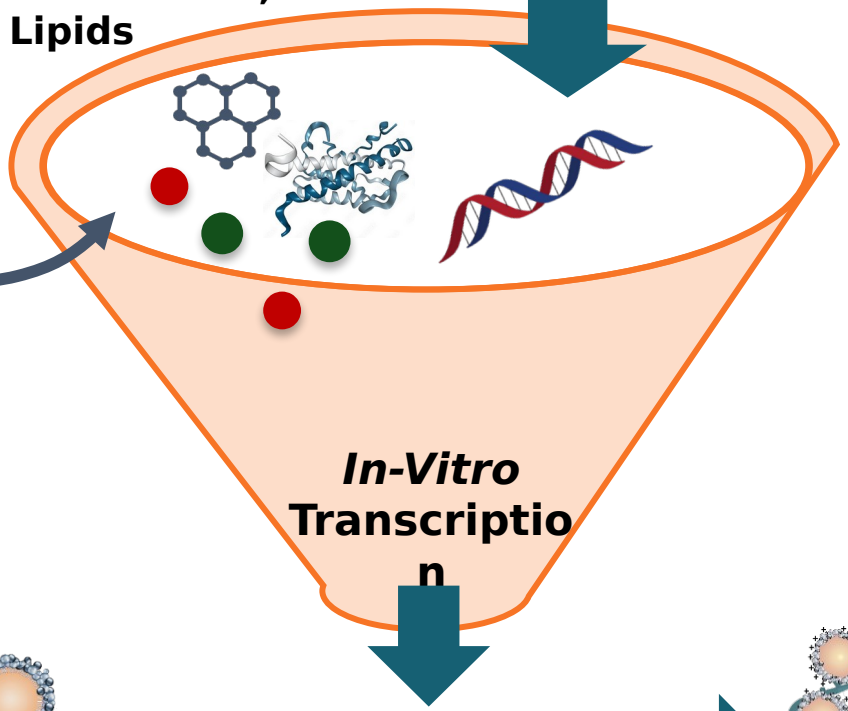
NATIONAL STOCKPILE

Cofactors, Enzymes, Nucleotides, Lipids

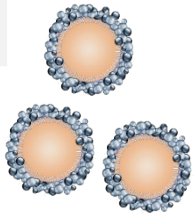
Antigenic DNA



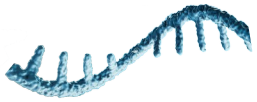
Change the Plasmid



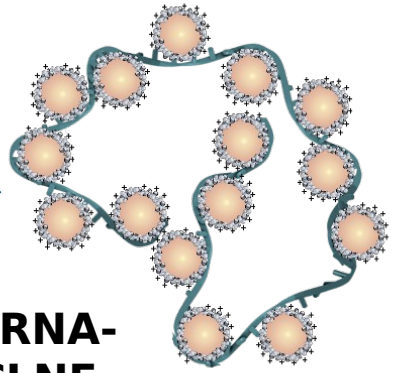
***In-Vitro* Transcription**



CLNE



mRNA



mRNA-CLNE complex

Our mRNA Vaccines

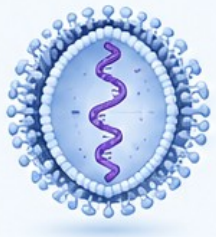
- GEMCOVAC®- 19
- GEMCOVAC®- OM

have been granted **Emergency Use Authorization**

mRNA VACCINES: SAFE, EFFECTIVE, ADAPTABLE

A Transformative Advance in Vaccinology with Enduring Impact for Public Health and Beyond

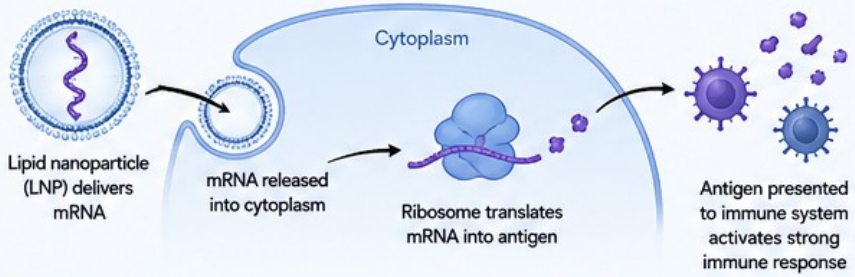
A TRANSFORMATIVE PLATFORM



- Rapid development timelines
- Scalable manufacturing
- Strong immunogenicity with favourable safety profile

Billions of doses administered globally during COVID-19 – unprecedented real-world evaluation across diverse populations.

HOW mRNA VACCINES WORK



- Transient cytoplasmic expression
- No genomic integration
- Rapid clearance from the body

Distinct from other gene therapies

SAFETY BY DESIGN & REGULATION

- Defined vaccine components (mRNA, LNP, excipients) with rigorous quality controls
- Robust manufacturing standards and lot-to-lot consistency
- Regulatory oversight by global authorities (e.g., FDA, EMA, CDSCO)
- Continuous safety monitoring and pharmacovigilance systems

CLINICAL EVIDENCE

- Randomised controlled trials demonstrated high efficacy and acceptable safety
- High efficacy against symptomatic disease, severe disease and hospitalisation
- Consistent safety profile across trials and age groups

REAL-WORLD EFFECTIVENESS

- Effectiveness across all age groups, including older adults and adolescents
- Protects during pregnancy
- Beneficial in immunocompromised populations

Reduces transmission and supports community protection

PUBLIC HEALTH IMPACT

- Saved millions of lives and prevented severe outcomes
- Reduced burden on healthcare systems
- Strengthened pandemic preparedness and health system resilience

PUBLIC PERCEPTION & CONFIDENCE

- Transparent communication
- Engagement with communities
- Addressing misinformation
- Building and sustaining trust

NEXT-GENERATION mRNA VACCINES: THE ROAD AHEAD

- Reduce reactogenicity and improve tolerability
- Broader and more durable immunity
- Enhanced global access and equity
- Sustainable public trust and confidence
- Expanding to cancer and autoimmunity

The accumulated evidence affirms mRNA vaccines as a safe, effective, and adaptable platform with enduring relevance for future infectious disease prevention and public health preparedness, and for the treatment of cancer and autoimmunity.

THE LANCET

The Lancet, vol. 408, issue 10551, pp. 275–288 (18 July 2026)

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info@immunoscript.bio

OFFICE

BTS-2 Building, Chrysalis Enclave, Block 2
International Biotech Park, Phase II
MIDC Hinjawadi, Pune 411057
Maharashtra, India

ImmunoScript Life Science Private Limited
CIN U72100PN2026PTC255053

SCAN TO VISIT

immunoscript.bio

FIOCRUZ RNA Platform

Patrícia Neves

Head of RNA Products Development/ ESPDT/VDINV
Bio-Manguinhos/ FIOCRUZ

FIOCRUZ SUS MINISTÉRIO DA SAÚDE GOVERNO FEDERAL BRASIL UNIÃO E RECONSTRUÇÃO

BRAZILIAN CONQUEST

Selected by WHO to be part of RNA Program

The Oswaldo Cruz Foundation has been selected by the World Health Organization (WHO)/Pan American Health Organization as one of the partner institutions in the RNA Program.

The selection is the result of a global call aimed at increasing the capacity for development and production and expanding access to RNA vaccines in low- and middle-income countries.


CNN BRASIL

"Já era esperado", diz Dalcolmo sobre escolha da OMS para Fiocruz fabricar vacina

Fundação vai desenvolver e produzir novo imunizante contra Covid-19 com tecnologia de RNA mensageiro (mRNA), na América Latina

Beatriz Puente e Thayana Araújo, da CNN, no Rio de Janeiro

26/09/21 às 08:58 | Atualizado 26/09/21 às 08:58

CNN 29 jun 2021


O GLOBO SAÚDE

Fiocruz é selecionada pela OMS para desenvolver vacina de RNA mensageiro

Instituto Bio-Manguinhos será centro para desenvolvimento e produção de imunizantes com essa tecnologia na América Latina

O Globo

21/09/2021 - 17:30 / Atualizado em 21/09/2021 - 18:42

Jornal O Globo 21 set 2021


exame.

Fiocruz é escolhida pela OMS para desenvolver vacina com técnica inovadora

Instituto Bio-Manguinhos será centro para desenvolvimento e produção de imunizantes com essa tecnologia na América Latina

Exame 21 set 2021


agênciaBrasil 35 anos

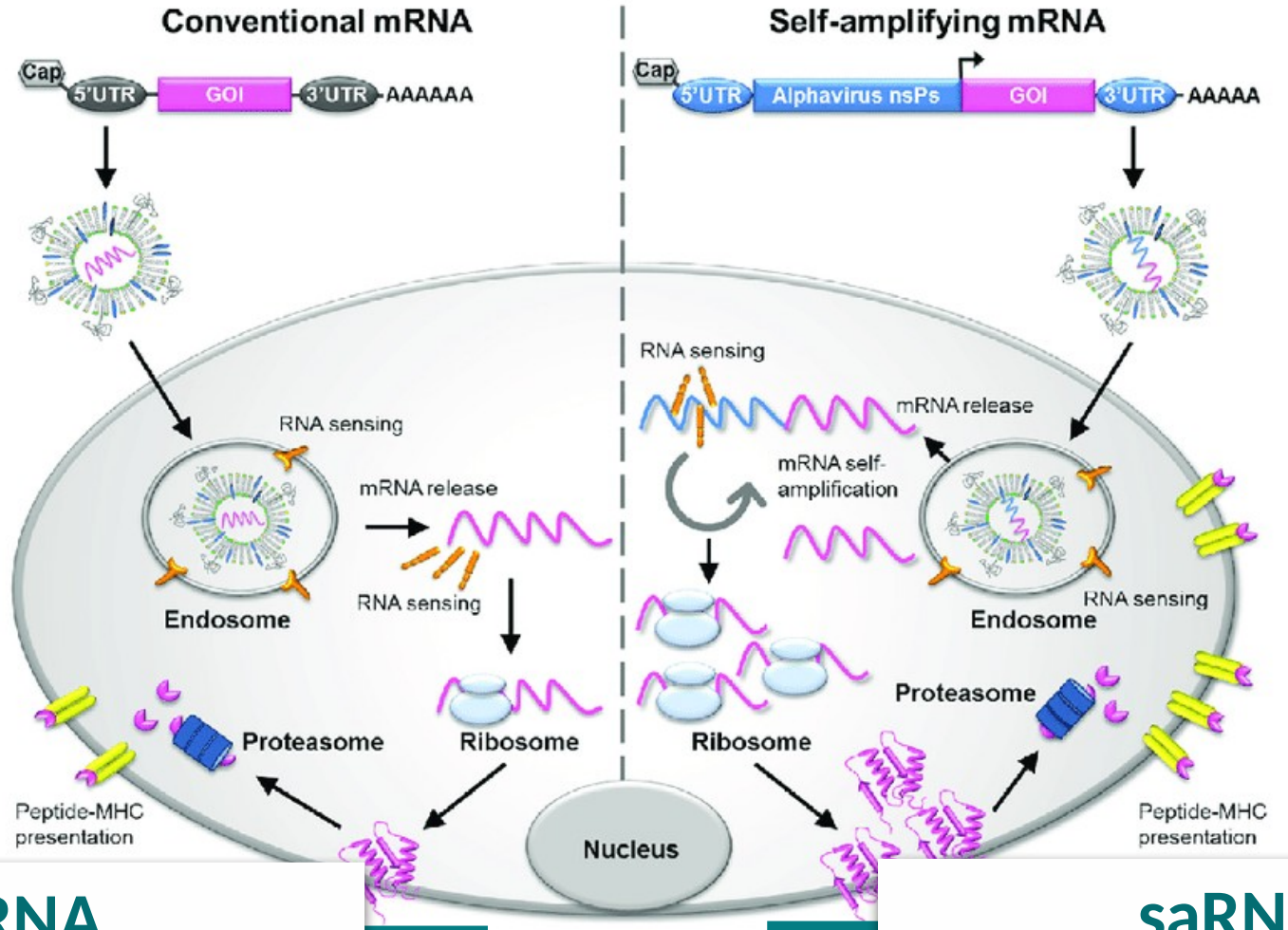
Saúde

OMS escolhe Fiocruz para produção de vacinas contra covid-19

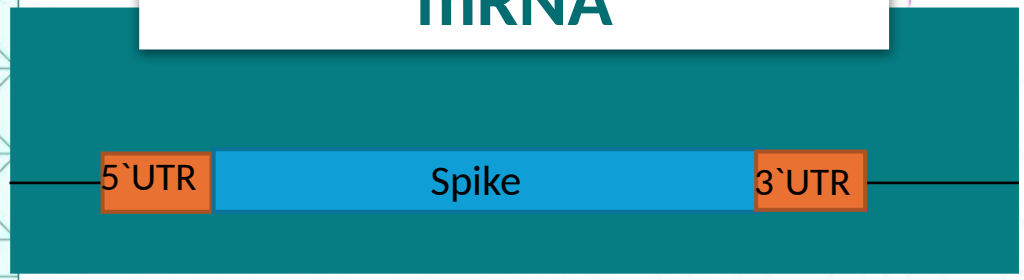
Vacinas de RNA mensageiro são um novo tipo de imunizante em estudo

Agência Brasil 21 set 2021

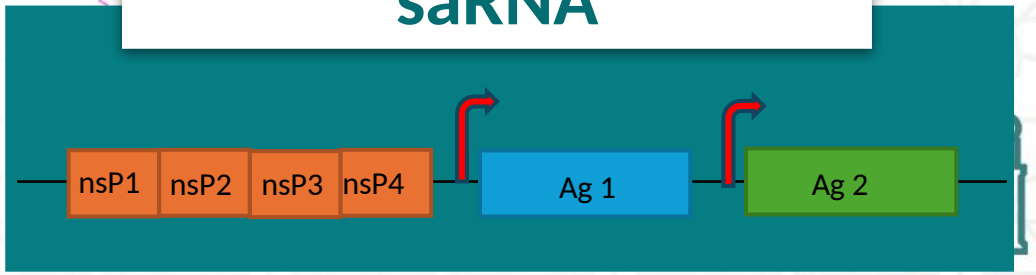
DEVELOPMENT STRATEGY



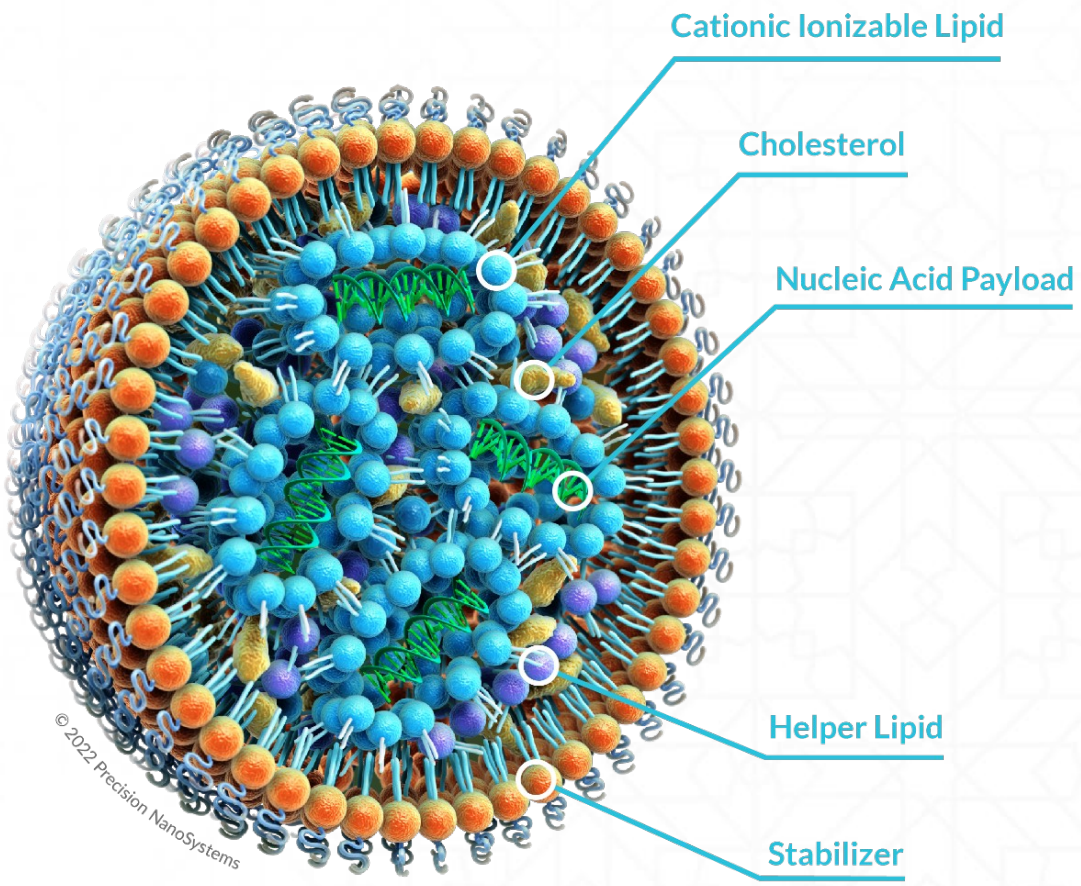
mRNA



saRNA



IONIZABLE LIPIDS



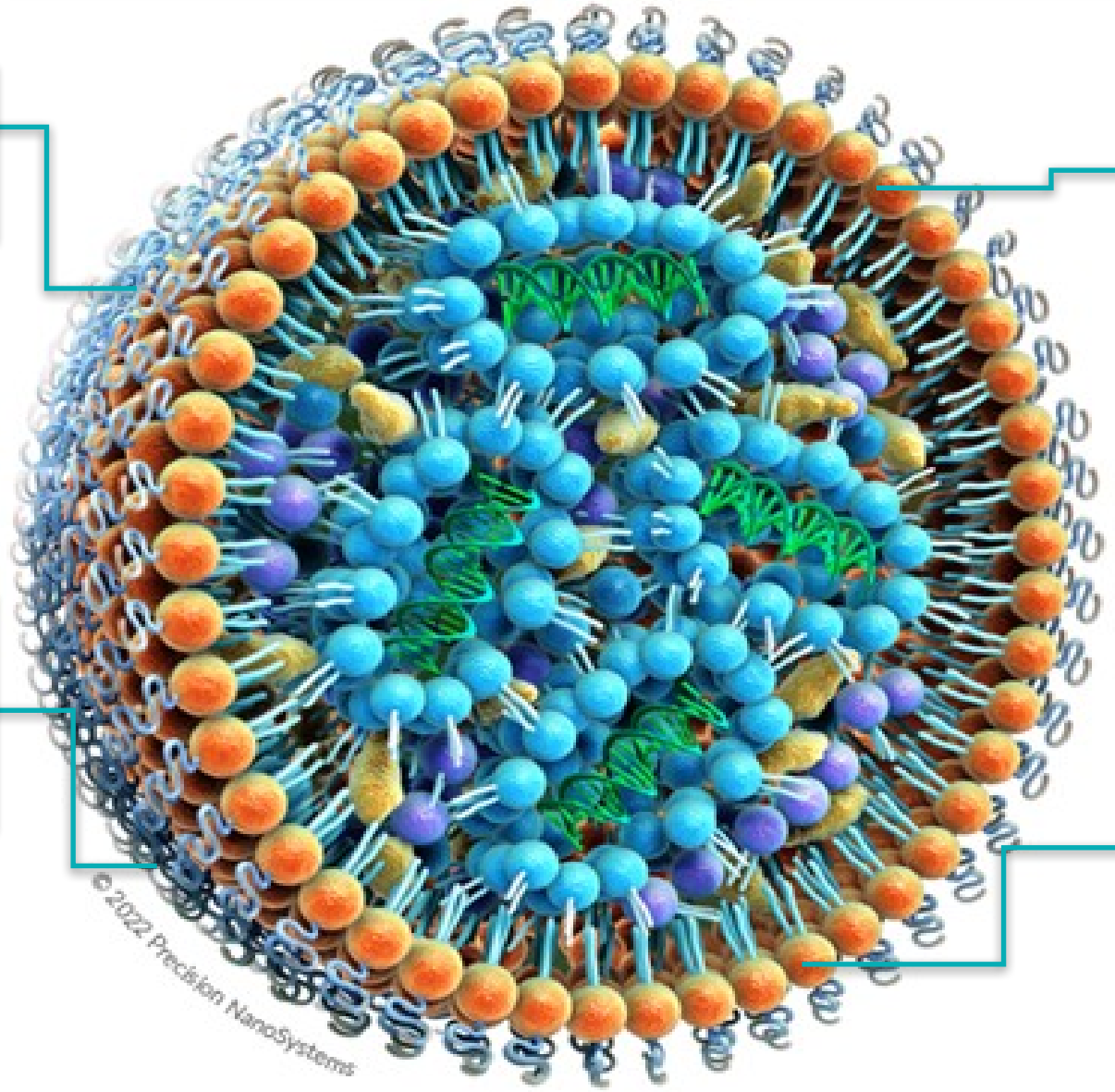
MORE THAN 20 COMBINATIONS

of ionizable lipids x constructs have been fully developed at Bio-Manguinhos

BRAZILIAN RNA PLATFORM

100 % protection

High titers of neutralizing antibodies



Robust T cell responses

Reduced Viral Load

BRAZILIAN RNA PLATFORM

"*Platform for the Expression of Non-Replicating (Conventional) Messenger RNA (mRNA) for the Development of Vaccines and Therapies: Nucleic Acid Sequence, Composition, Use, Method of Treatment and/or Prevention of Diseases and Method of Preparation of the Composition*"

PCT_BR_2025_050533

Denis Barbosa Award for Intellectual Property and Public Interest

Brazilian RNA Vaccines- Manufacturing

First GMP area for RNA products in Latin America

Brazilian RNA Vaccines- Manufacturing

To achieve large-scale production using GMP inputs, Bio-Manguinhos uses equipment called Ntensify Midi from QUANTOOM.

System Functions
(Divided into Two Parts)

- Performs mRNA production using IVT technique
- Performs mRNA purification using magnetic beads

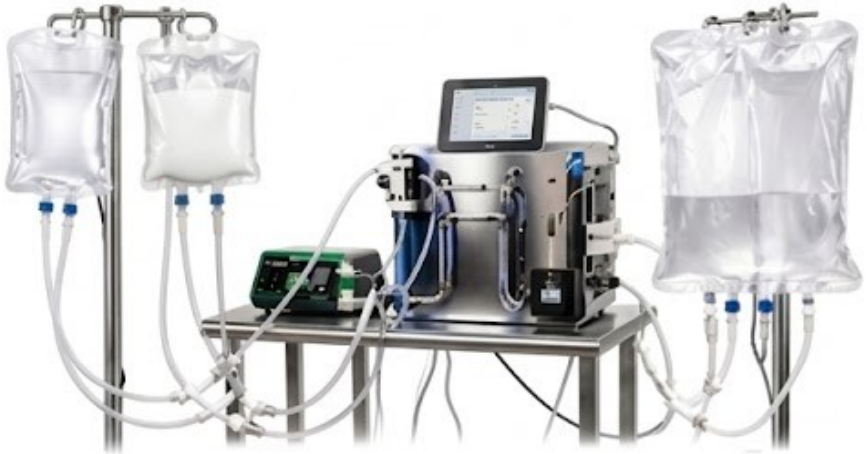
Processing Time

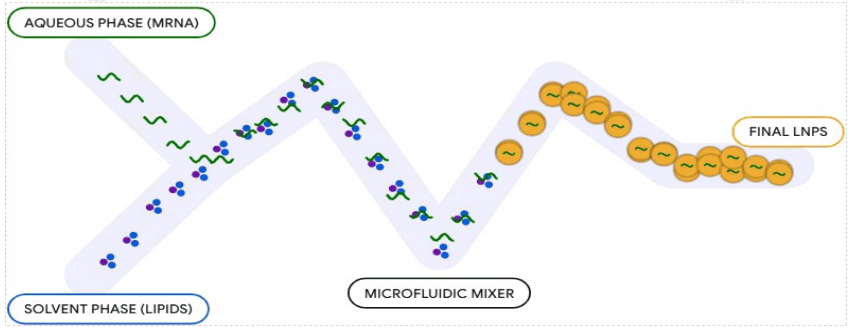
- Installation: 2 hours
- Calibration: 1:30 min
- Start-up: 5 hours for 1 reactor or 12 hours for 4 reactors.

1 reactor	4 reactors
1g mRNA purified	4g mRNA purified
~around 10,000 doses of vaccine	~around 40,000 doses of vaccine

Brazilian RNA Vaccines- Manufacturing

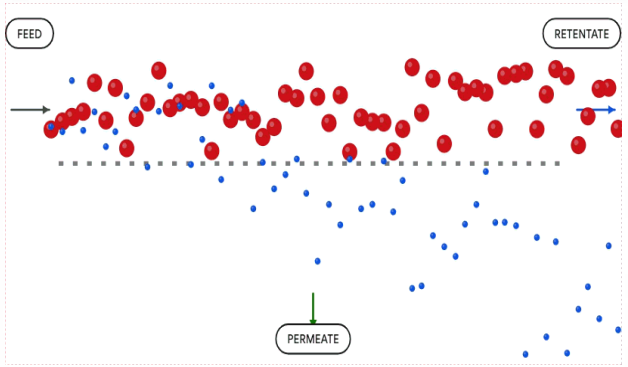
ENCAPSULATION
(formation of mRNA-LNPs)





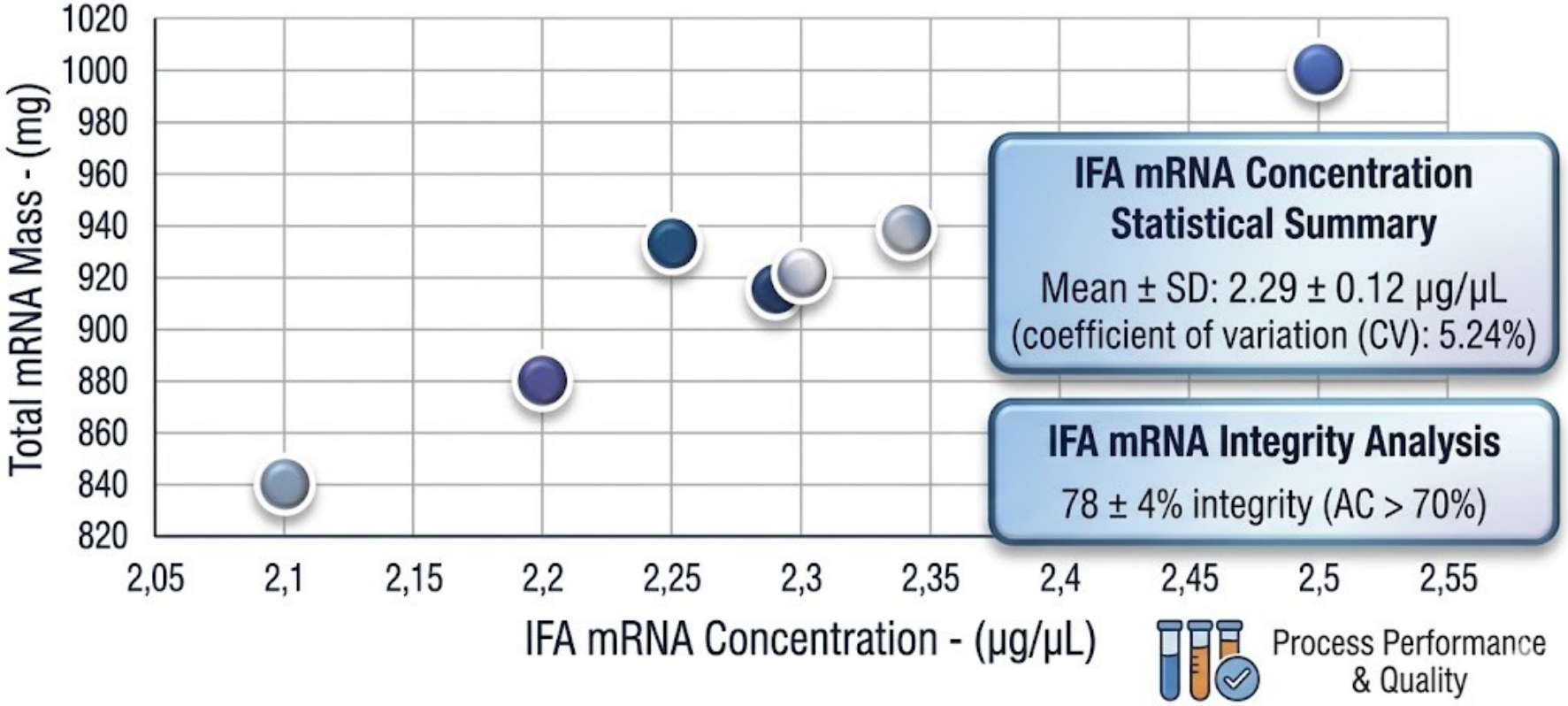
In a microfluidic mixer, the aqueous phase (mRNA) is rapidly mixed with the solvent phase (lipids), leading to the self-assembly of lipids around the mRNA to form LNPs.

TFF (TANGENTIAL FLOW FILTRATION)
(Purification and Concentration)

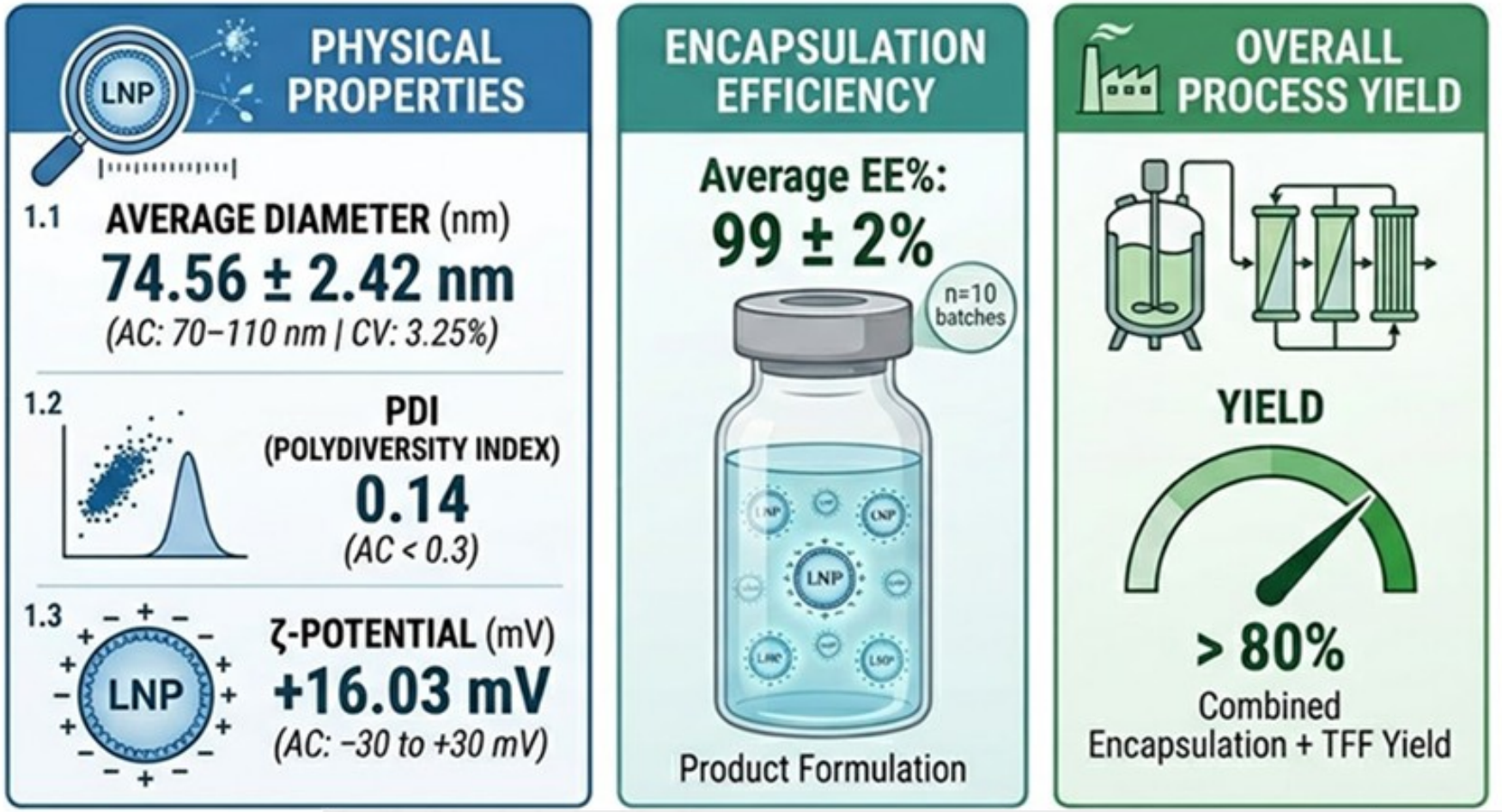


TFF uses tangential flow to keep particles in the retentate while allowing buffer and small molecules to pass through the membrane (permeate).

Brazilian RNA Vaccines- Manufacturing



Brazilian RNA Vaccines- Manufacturing



Brazilian RNA Vaccines- Manufaturing Capacity

Naked RNA (DS)

Encapsulation

Fill and Finish (DP)

Housing

TOX Studies

BIONEEDS
A Veeda Lifesciences Company

No. : SPR004/25
Date: 09/05/2025

STUDY PROGRESS REPORT

Treatment: The respective group animals received test item at specified dose as indicated under 'Study Design', whereas the animals of G1/G1R received control (saline) and G2/G2R received vehicle control (LNP) alone through intramuscular route.

Clinical signs of toxicity/mortality: No treatment related clinical signs of toxicity or mortality were noted in all the tested group animals. However, injection site thickening was observed in all animals except control (saline) group.

Refer Table 1.

Body Weight: Slight decrease in body weight was observed in treated males (G2/G2R, G3/G3R & G4/G4R) when compare to saline control group males (G1/G1R).

Refer Table 2.

Feed Consumption: Slight decrease in feed consumption was observed in treated males (G2/G2R, G3/G3R & G4/G4R) when compare to saline control group males (G1/G1R).

Refer Table 3.

Assessment of Local Reaction: No local skin reactions like erythema and edema at injection site were observed in any of the treated group animals till today.

Refer Table 4.

Physiological Observation (Body Temperature):

After first administration, vaccine and LNP related increase in rectal temperature of >38°C up to day 3 was noted in G2/G2R, G3/G3R & G4/G4R group animals and returned to normal from day 4. After second dose administration, vaccine and LNP related increase in rectal temperature >38°C was noted on day 18 in G2/G2R, G3/G3R & G4/G4R group animals. After third dose administration, vaccine and LNP related increase in rectal temperature >38°C was noted on day 32 in G2R, G3R & G4R group animals. ((main group animals (G2, G3 & G4) shown rectal temperature >38°C on day 30 and day 31)).

QUALITY AND REGULATORY DEVELOPMENT

FIOCRUZ

SUS

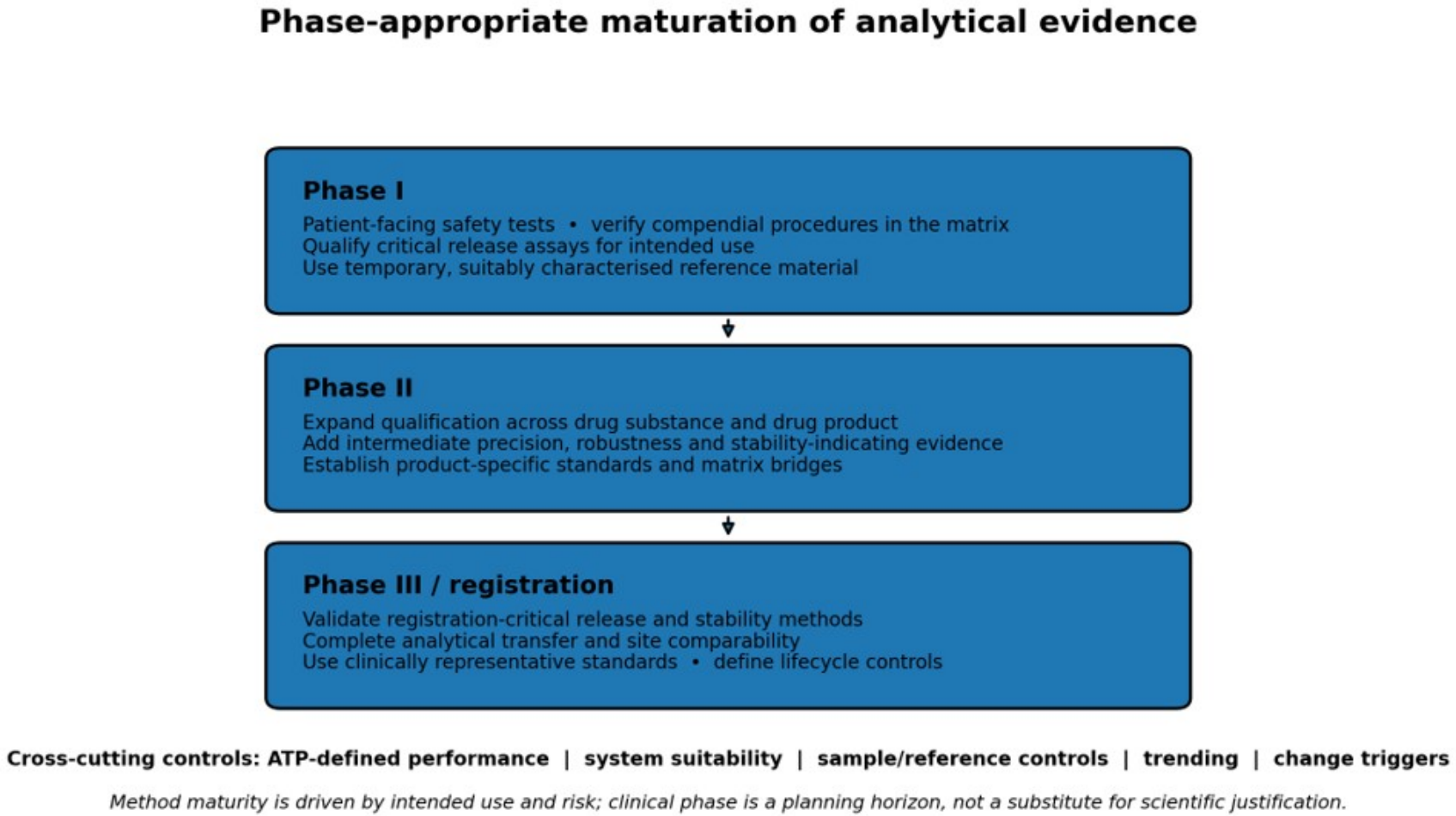
MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL

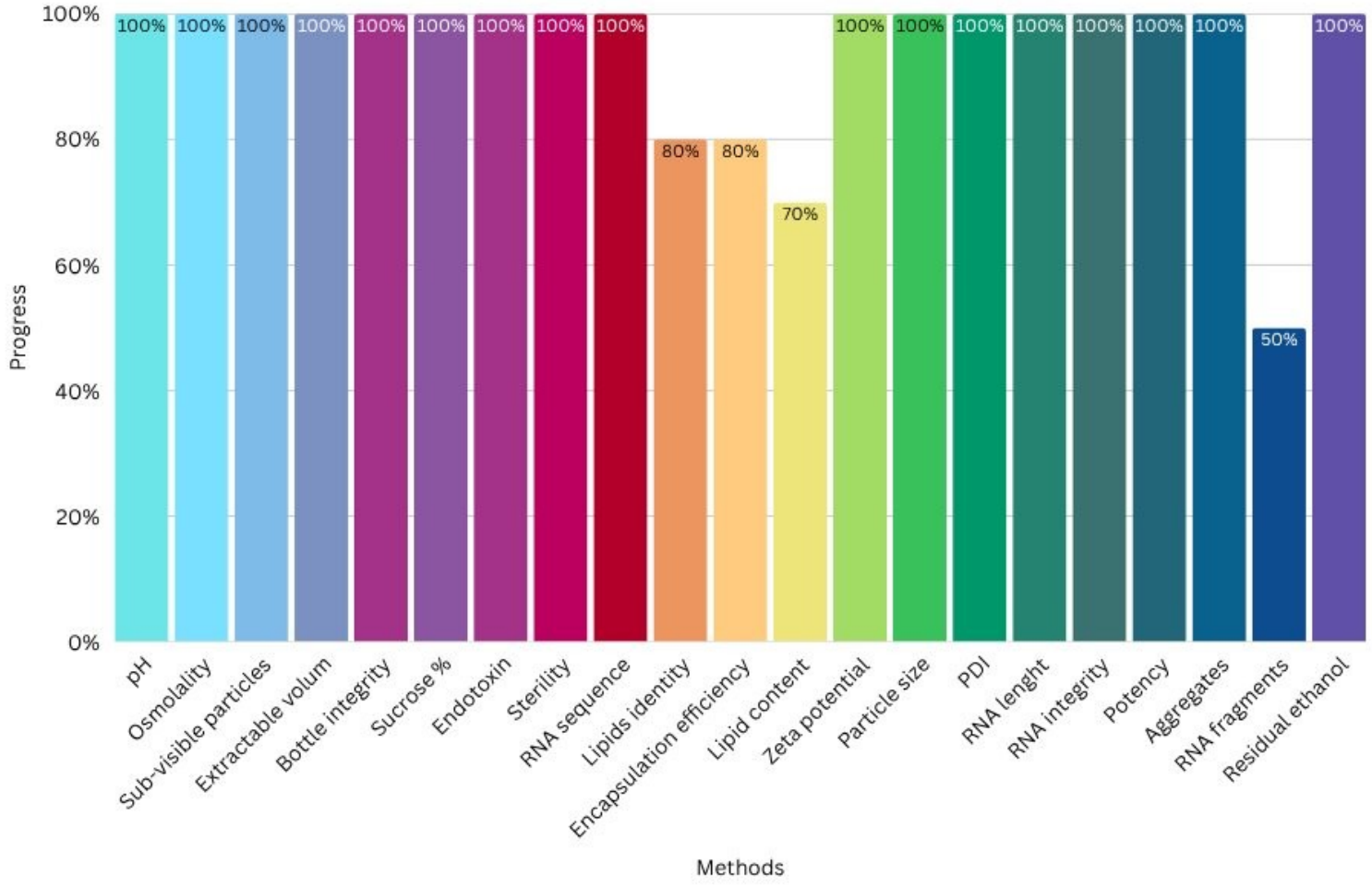
BRASIL

UNIÃO E RECONSTRUÇÃO

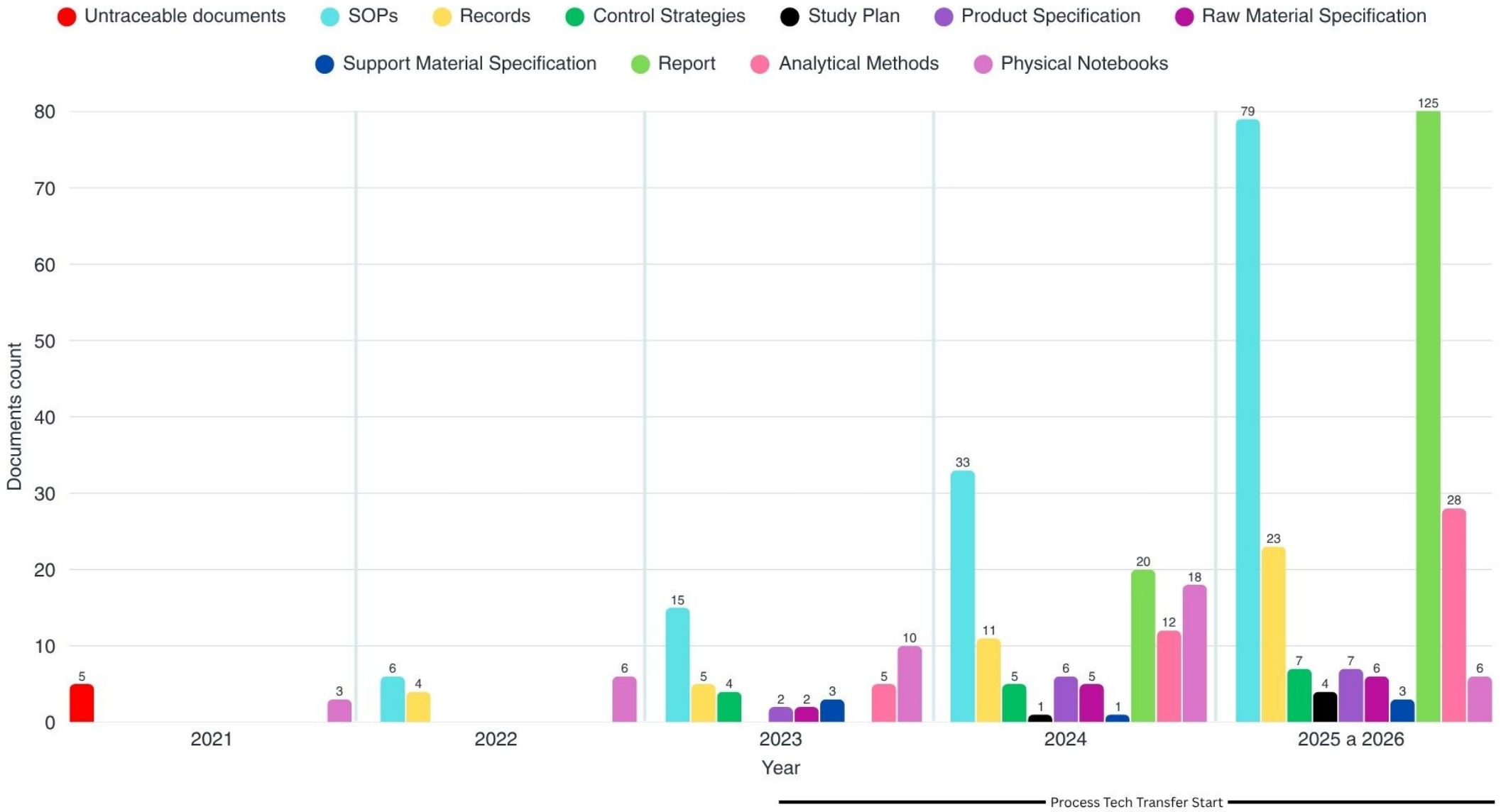
Analytical Control Strategy



Quality Control Status- DP controls



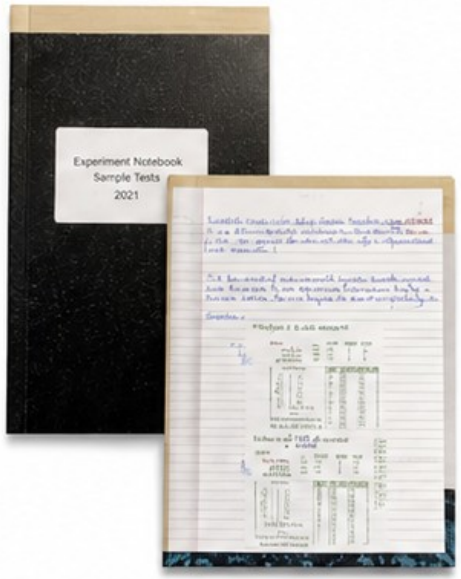
Documentation Status



de Tecnologia
obiológicos
Manguinhos

Records

2021



Ordinary notebook,
low traceability

2022

Ministry of Health
FIOCRUZ
Institute of Technology in Immunobiologicals

TECHNICAL RECORD OF IN VITRO RNA TRANSCRIPTION

DI No. 2022/00045
Page 01 of 01

Record number:	Date:	Responsible:

Sample identification

Product:
Batch/Lot:
Sample type: ☐ Raw material ☐ In-process ☐ Other:
Origin: Quantity:
Storage condition: Expiration date:

Test information

Test:
Method:
Equipment: Analyst:
Test on: Supervisor:

Results / Observations:

Reagents and Materials

Item	Code	Lot	Manufacturer	Expiration date	Qty	Unit
Item 1	12345	ABC123	Manufacturer A	12/2003	1	mL
Item 2	67890	XYZ456	Manufacturer B	05/2024	1	mL

Prepared by:	Checked by:	Approved by:

Records with DI number,
experimental notebooks,
with traceability

2023 and 2024

Ministry of Health
FIOCRUZ
Institute of Technology in Immunobiologicals

RECORD BPx

BPx RECORD OF IN VITRO PLASMID DNA PRODUCTION

Registry No.: BPx/23_0001AM	Confidential	Page 01 of 01
Unit Resp.: DEDP LATIM	Name: BPx/23_0001AM	Cost center:

Document type: PRODUCTION RECORD – PLASMID DNA (IN VITRO)

1. GENERAL INFORMATION

Product:	Batch/Lot:
Start date:	End date:
Start time:	End time:
Analyst:	Supervisor:
Equipment in use:	Location:

Scope of work:
Plasmid DNA production (in vitro)
Extraction of plasmid DNA

2. DAILY RECORD

Step:	Start time:	End time:	
Duration:			
Deviations: ☐ Yes ☐ No	Description:		
Responsible person:	Signature:	Date:	
Review by:	Signature:	Review date:	

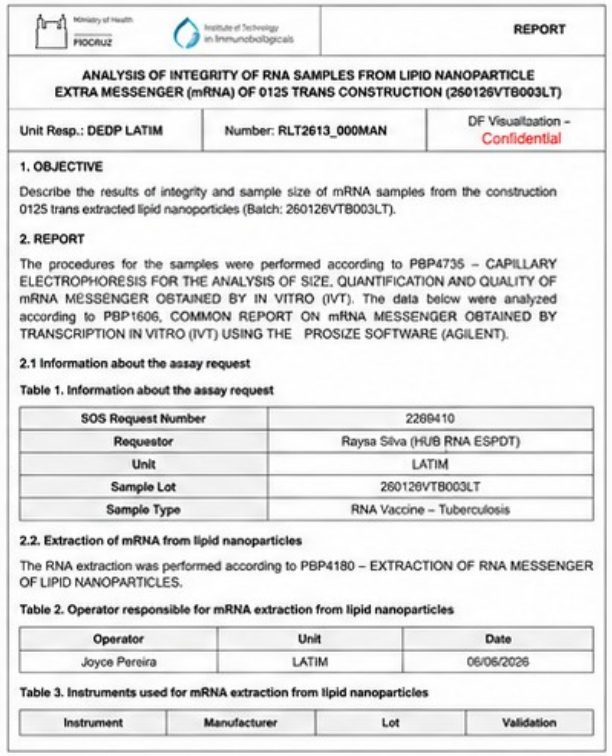
3. EQUIPMENT

Equipment	Code	Phase	Tag
Equipment 1	EQ-01	Phase 2	TAG001
Equipment 2	EQ-02	Phase 2	TAG002
Equipment 3	EQ-03	Phase 3	TAG003
Equipment 4	EQ-04	Phase 3	TAG004
Equipment 5	EQ-05	Phase 3	TAG005

Printed by: Date:	Date: 01/05/2023	Version: 01	Page: 1 of 1

BPx records, formalized,
with traceability,
printed and bound

2025 to date



Ministry of Health
FIOCRUZ
Institute of Technology in Immunobiologicals

REPORT

ANALYSIS OF INTEGRITY OF RNA SAMPLES FROM LIPID NANOPARTICLE EXTRA MESSENGER (mRNA) OF 0125 TRANS CONSTRUCTION (260126VTB003LT)

Unit Resp.: DEDP LATIM	Number: RLT2613_000MAN	DF Visualization – Confidential

1. OBJECTIVE

Describe the results of integrity and sample size of mRNA samples from the construction 0125 trans extracted lipid nanoporticles (Batch: 260126VTB003LT).

2. REPORT

The procedures for the samples were performed according to PBP4735 – CAPILLARY ELECTROPHORESIS FOR THE ANALYSIS OF SIZE, QUANTIFICATION AND QUALITY OF mRNA MESSENGER OBTAINED BY IN VITRO (IVT). The data below were analyzed according to PBP1606, COMMON REPORT ON mRNA MESSENGER OBTAINED BY TRANSCRIPTION IN VITRO (IVT) USING THE PROSIZE SOFTWARE (AGILENT).

2.1 Information about the assay request

Table 1. Information about the assay request

SOS Request Number	2269410
Requestor	Raysa Silva (HUB RNA ESPDT)
Unit	LATIM
Sample Lot	260126VTB003LT
Sample Type	RNA Vaccine – Tuberculosis

2.2. Extraction of mRNA from lipid nanoparticles

The RNA extraction was performed according to PBP4180 – EXTRACTION OF RNA MESSENGER OF LIPID NANOPARTICLES.

Table 2. Operator responsible for mRNA extraction from lipid nanoparticles

Operator	Unit	Date
Joyce Pereira	LATIM	06/06/2026

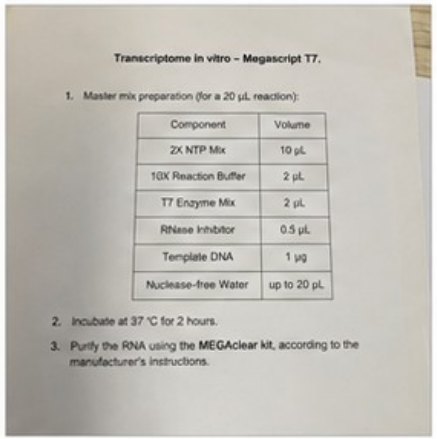
Table 3. Instruments used for mRNA extraction from lipid nanoparticles

Instrument	Manufacturer	Lot	Validation

Highly detailed
analysis records

SOPs, analytical methods, reports

2021



Transcriptome in vitro – Megascript T7.

1. Master mix preparation (for a 20 µL reaction):

Component	Volume
2X NTP Mix	10 µL
10X Reaction Buffer	2 µL
T7 Enzyme Mix	2 µL
RNase Inhibitor	0.5 µL
Template DNA	1 µg
Nuclease-free Water	up to 20 µL

2. Incubate at 37 °C for 2 hours.
3. Purify the RNA using the MEGAclear kit, according to the manufacturer's instructions.

Informal protocols, without traceability, printed version

2022

WORK INSTRUCTION

TITLE: IN VITRO RNA TRANSCRIPTION

DI No.: LAT102

REVISION: 00

1. CHANGES

Revision	Date	Change
00	02/11/2022	Issue

2. OBJECTIVES

Describe the procedures for in vitro RNA transcription using the MEGAscript T7 kit.

3. SCOPE OF APPLICATION

Applies to the Immunology Technology Laboratory – LATIM, at the Technology Development Vice-Presidency – VDTEC.

Protocols with DI number, formalized, with traceability, printed

2023 and 2024

Ministry of Health
FIOCRUZ
Bio-Manguinhos Institute

STANDARD OPERATING PROCEDURE (SOP)

OBTAINING IN VITRO TRANSCRIBED RNA

RESP. UNIT: DEDEP LATIM	Document No.: PPAT79_000MAN	PDF Visualization: Confidential

1. OBJECTIVE

Describe the procedures for obtaining planned DNA from bacterial strains transformed with plasmids for transcription in vitro.

2. SCOPE

Applies to the Immunology Technology Laboratory – LATIM, at the Experimental Department and Pre-clinical – DEDEP, of the Innovation Vice-Presidency – VDIn.

SOPs in BPx, formalized, with traceability, printed and digital (StarDoc)

2025 to date

Ministry of Health
FIOCRUZ
Bio-Manguinhos Institute

REPORT

REPORT ON THE EVALUATION OF THE ELECTROPHORESIS METHOD FOR DETERMINING THE SIZE AND INTEGRITY OF mRNA ENCAPSULATED IN LIPID NANOPARTICLES

RESP. UNIT: DEDEP LATIM	Report No.: RLT2544_000MAN	PDF Visualization: Confidential

Ministry of Health
FIOCRUZ
Bio-Manguinhos Institute

ANALYTICAL METHOD

INTEGRITY ANALYSIS METHOD OBTAINED FROM mRNA BY IN VITRO TRANSCRIPTION (IVT) OF THE COVID-19 VACCINE BY CAPILLARY ELECTROPHORESIS

RESP. UNIT: DEDEP LATIM	Document No.: MTA066_001MAN	PDF Visualization: Confidential

Ministry of Health
FIOCRUZ
Bio-Manguinhos Institute

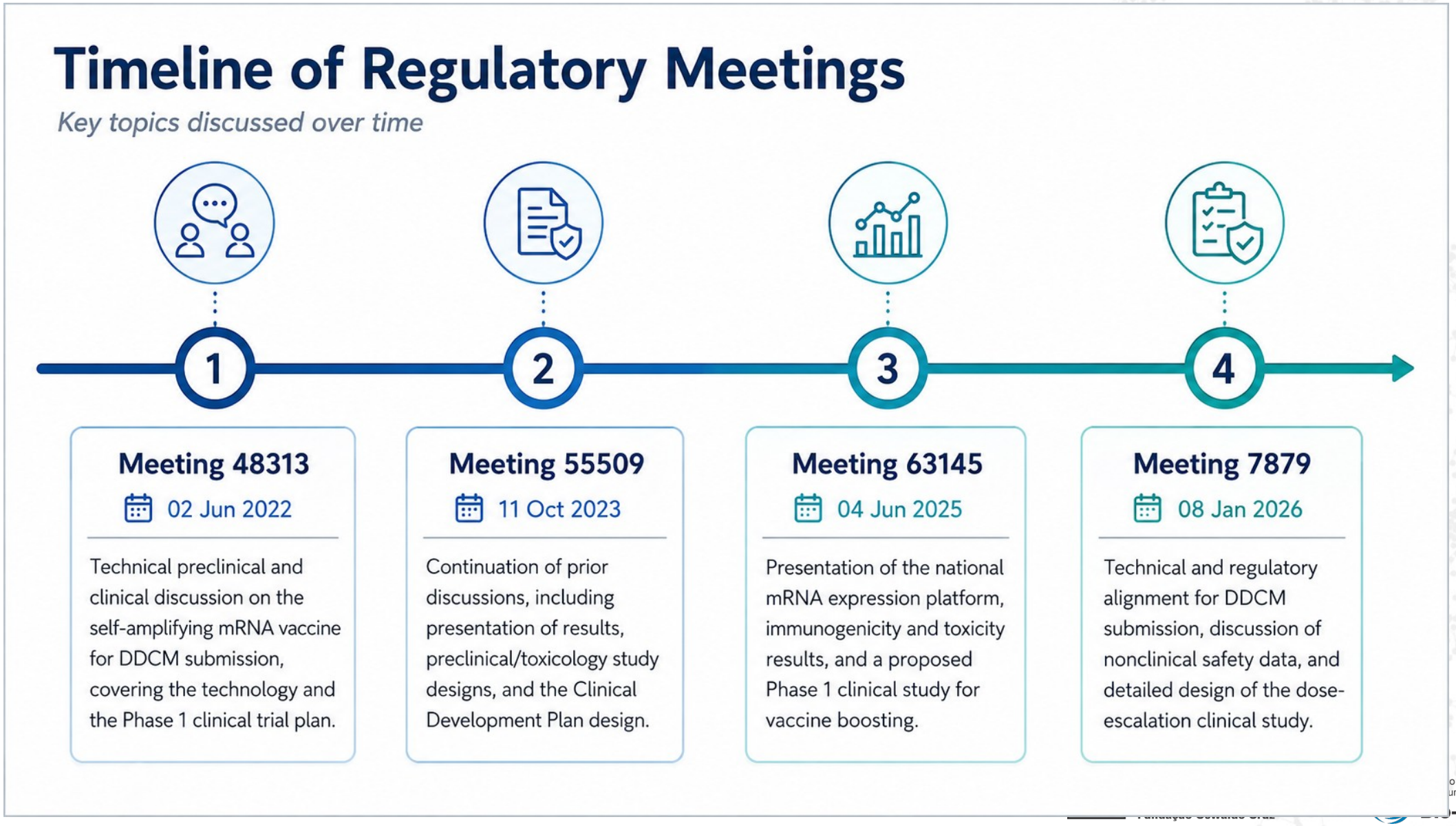
REPORT

ANALYSIS OF THE INTEGRITY AND SIZE OF EXTRACELLULAR mRNA SAMPLES OF LIPID NANOPARTICLES - TUBERCULOSIS/012S TRANS (260128VTB003LT)

RESP. UNIT: DEDEP LATIM	Report No.: RLT2613_000MAN	PDF Visualization: Confidential

In addition to SOPs,
we now have QC and stability
analysis reports available in real time

Dialogue with ANVISA



IND submission- Phase I request

Comprovante de Protocolização Page 1 of 1

ANVISA

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA
Unidade de Atendimento e Protocolo - UNIAP
Impresso em: 13/02/2026 21:47:10

COMPROVANTE DE PROTOCOLIZAÇÃO ON-LINE

Protocolo:
20260000000138243
Expediente:
0153513267
Número de Transação:
2089342026
Tipo de Documento:
Processo
Número do Processo:
25351029069202611
Favorecido:
33.781.055/0001-35 - FUNDACAO OSWALDO CRUZ
Assunto:
10754 - ENSAIOS CLÍNICOS - Anuência em processo do Dossiê de Desenvolvimento Clínico de Medicamento (DDCM) - Produtos Biológicos

Protocolizado On-Line via Peticionamento Eletrônico por:
136.231.107-36 - CELINA VIEIRA DA CUNHA GUEDES ALVARENGA em 13/02/2026 21:47:10

Requirements answered in July 1st 2026

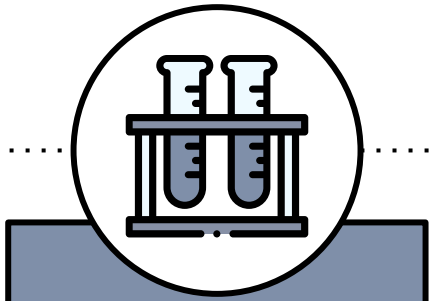
BRAZILIAN RNA PLATFORM

Early Development

- Antigen design
- RNAm backbone
- Formulation development

Proof of Principle

- Pilot scale production
- Non-clinical lots
- Animal tests



Scaling up

- Scaling up studies
- Process improvements

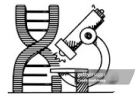
GMP production

- Clinical batches production

Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz

Instituto de Tecnologia em Imunobiológicos
Bio-Manguinhos

PORTFÓLIO – RNA

TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
								
Discovery	*Hypotesis*	*Proof of Concept*	*Validation Lab.*	*Scaling up*	*Clinical Trials*			*Register*

- RNA-Covid
- RNAi – synthetic
- Tuberculosis
- Leishmanisis
- Oropouche Vaccine
- Yellow Fever Vaccine
- Mpox Vaccine
- Therapeutic Vaccines
- anti-PD1 RNA
- In vivo CART

- **RNA Network**
- **Thermostability**

RNA PLATFORM: REGULATORY QUALIFICATION FRAMEWORK

International references and convergent evidence requirements | Status: July 2026

REGULATORY LANDSCAPE

FDA · 2024 DRAFT	WHO · 2022	EMA · 2025 DRAFT	PMDA · 2026	MHRA · 2025 DRAFT	ICH FRAMEWORK	EU vPTMF
Formal designation program for human drugs and biologics	mRNA/saRNA-LNP vaccine platform approach	Human mRNA quality and prior-knowledge approach	Nonclinical platform-based safety bridging	Fixed/variable model for individualised mRNA	Q8, Q9, Q10, Q11 and Q12	Formal certification — veterinary vaccines only

CONVERGENT REQUIREMENTS TO QUALIFY AS AN RNA PLATFORM

1 Defined Platform Boundary

Clearly distinguish the fixed technological core from the variable RNA payload.

2 Anchor Product & Cross-Product Evidence

Use an approved or qualified reference product and relevant data across more than one product.

3 Standardised and Reproducible Manufacturing

Apply the same core process, equipment strategy and validated operating ranges.

4 QTPP, CQAs, CPPs & Specifications

Define product targets, critical attributes, process parameters and a robust control strategy.

5 Comparable Formulation & Delivery

Maintain the delivery system and formulation, or demonstrate scientifically justified comparability.

6 Comparable Impurities, Stability & Performance

Show that payload changes do not materially alter quality, impurity clearance or stability.

7 Risk-Based Bridging + Product-Specific Tests

Leverage platform knowledge while retaining identity, potency and on-target safety assessments.

8 Lifecycle Governance & Change Management

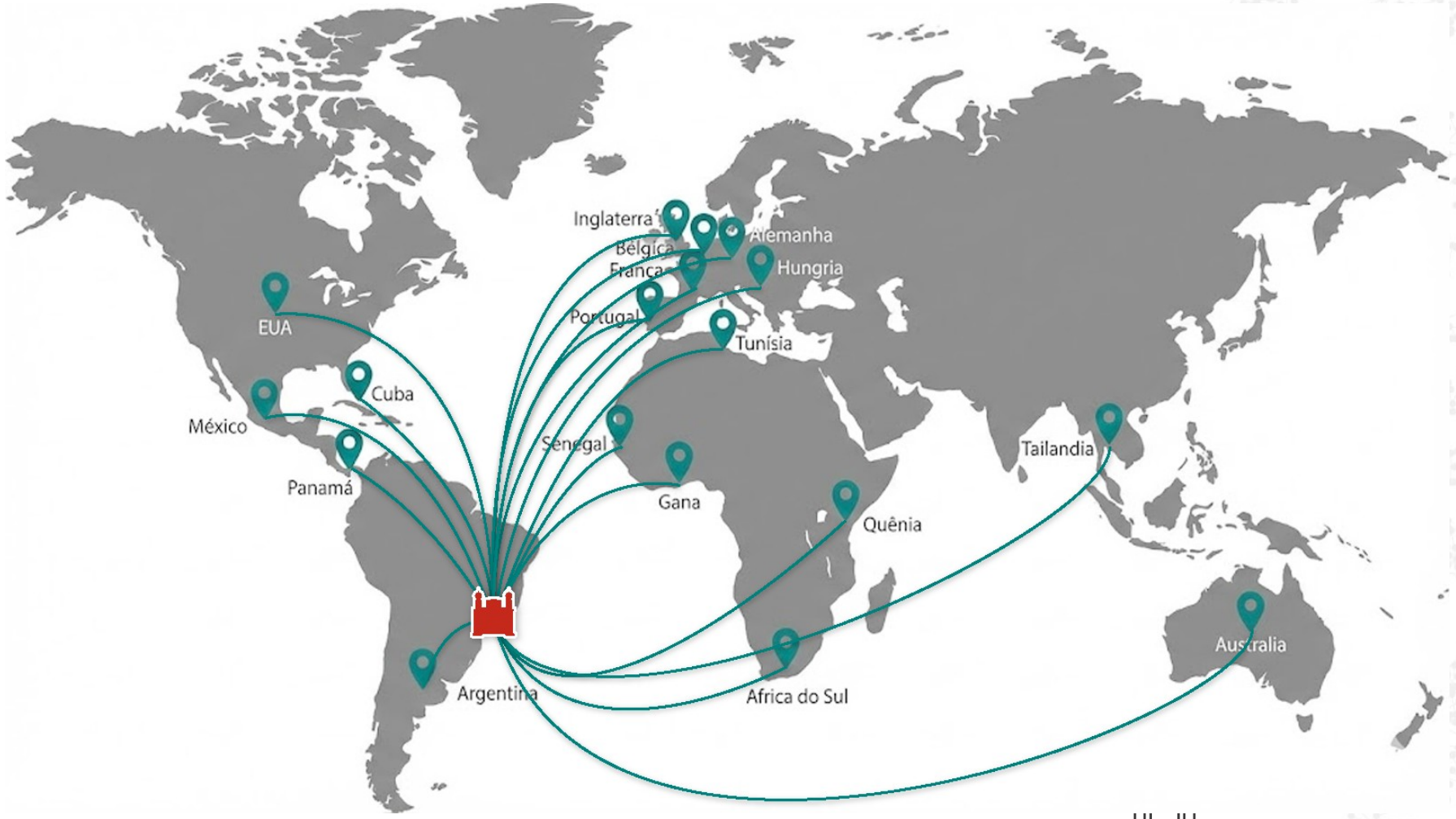
Use comparability protocols, knowledge management, decision gates and controlled platform evolution.

PLATFORM-READY FOR REGULATORY DATA LEVERAGING

Formal designation depends on jurisdiction: FDA — human drugs and biologics; EU vPTMF — veterinary vaccines.

WHO, EMA, PMDA and MHRA use platform or prior-knowledge approaches. A shared facility or common IVT equipment alone is not a regulatory platform.

FIOCRUZ: HUB FOR LATIN AMERICAN RNA INNOVATION ECOSYSTEM



FIOCRUZ
Fundação Oswaldo Cruz

Instituto de Tecnologia em Imunobiológicos
Bio-Manguinhos

Patrícia Neves

Leader of RNA Products Development

E-mail | **pcristina@bio.fiocruz.br**

Financers- Funds Raising Office FIOCRUZ

SUS

Gates Foundation

CEPI

Pan American Health Organization

BNDES

KFW DEG

AMBEV Drogasil

Repsol Shell

medicines patent pool

Ministério da Saúde

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Fundação Oswaldo Cruz

Instituto de Tecnologia em Imunobiológicos

Bio-Manguinhos

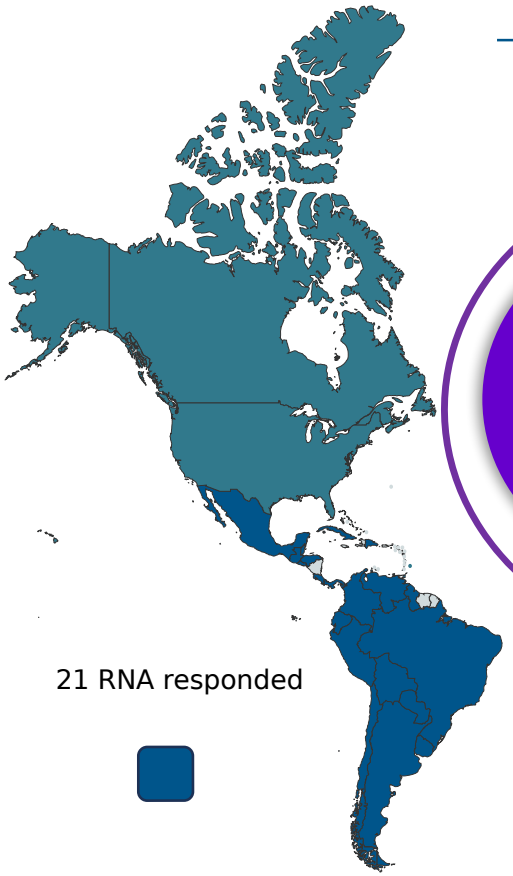
"The current emergency environment: how the regulatory landscape has evolved since COVID-19, and what is expected for the next emergency"

Strengthening Regulatory Preparedness in the Americas: Lessons from COVID-19 and Emerging Expectations for Future Vaccine Authorization

María Teresa Ibarz M.
International consultant to the Quality and Regulation Unit of Medicines and Health Technologies (QR), Department of Innovation, Access to Medicines and Health Technologies (IMT)

Lessons learned from the H1N1 pandemic and gaps identified in readiness for the introduction of COVID-19 vaccines

Mapping 2020



21 RNA responded

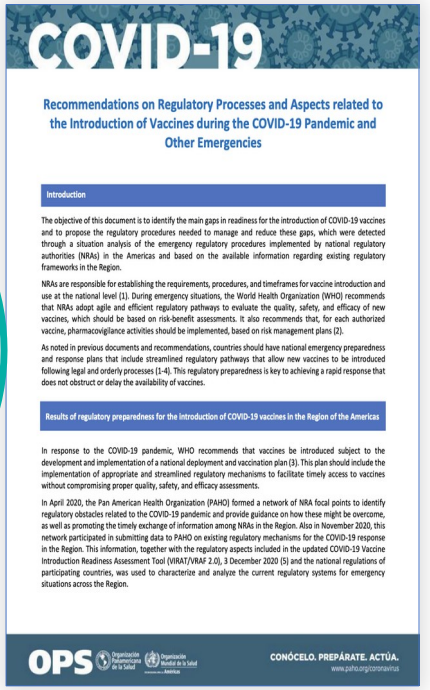
Existence of regulatory frameworks with **a traditional approach**.

Absence of regulatory requirements and procedures based on **risk criteria**.

Application of **exception pathways** without considering the type of medical product, origin and regulatory impact.

Lack of clarity in **roles and responsibilities** of the staff in charge.

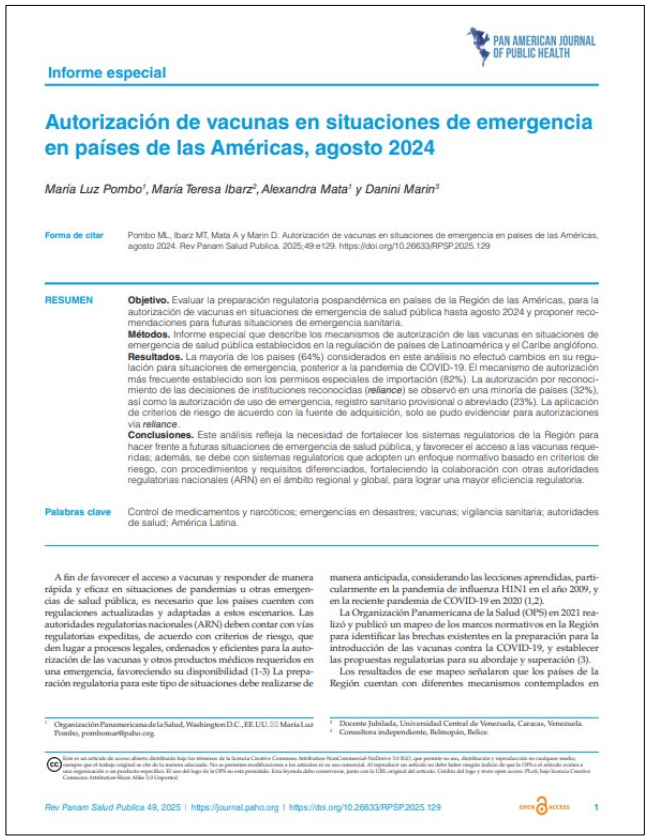
Lack of regulatory preparedness for emergencies.



1. WHO. Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries. TRS. 1004, 2017. https://apps.who.int/medicinedocs/documents/s23326en/s23326en.pdf
2. PAHO. Recommendations on Regulatory Processes and Aspects related to the Introduction of Vaccines during the COVID-19 Pandemic and Other Emergencies. 2021. https://iris.paho.org/handle/10665.2/54516

Authorization of vaccines and other medical products in emergency situations in the Region of the Americas

Mapping 2024



PAN AMERICAN JOURNAL OF PUBLIC HEALTH

Informe especial

Autorización de vacunas en situaciones de emergencia en países de las Américas, agosto 2024

María Luz Pombo[1], María Teresa Ibarz[2], Alexandra Mata[1] y Danini Marin[3]

Forma de citar Pombo ML, Ibarz MT, Mata A y Marin D. Autorización de vacunas en situaciones de emergencia en países de las Américas, agosto 2024. Rev Panam Salud Publica. 2025;49:e129. https://doi.org/10.26633/RPSP.2025.129

RESUMEN

Objetivo. Evaluar la preparación regulatoria pospandémica en países de la Región de las Américas, para la autorización de vacunas en situaciones de emergencia de salud pública hasta agosto 2024 y proponer recomendaciones para futuras situaciones de emergencia sanitaria.
Métodos. Informe especial que describe los mecanismos de autorización de las vacunas en situaciones de emergencia de salud pública establecidos en la regulación de países de Latinoamérica y el Caribe anglófono.
Resultados. La mayoría de los países (64%) considerados en este análisis no efectuó cambios en su regulación para situaciones de emergencia, posterior a la pandemia de COVID-19. El mecanismo de autorización más frecuente establecido son los permisos especiales de importación (82%). La autorización por reconocimiento de las decisiones de instituciones reconocidas (*reliance*) se observó en una minoría de países (32%), así como la autorización de uso de emergencia, registro sanitario provisional o abreviado (23%). La aplicación de criterios de riesgo de acuerdo con la fuente de adquisición, solo se pudo evidenciar para autorizaciones vía *reliance*.
Conclusiones. Este análisis refleja la necesidad de fortalecer los sistemas regulatorios de la Región para hacer frente a futuras situaciones de emergencia de salud pública, y favorecer el acceso a las vacunas requeridas; además, se debe con sistemas regulatorios que adopten un enfoque normativo basado en criterios de riesgo, con procedimientos y requisitos diferenciados, fortaleciendo la colaboración con otras autoridades regulatorias nacionales (ARN) en el ámbito regional y global, para lograr una mayor eficiencia regulatoria.

Palabras clave Control de medicamentos y narcóticos; emergencias en desastres; vacunas; vigilancia sanitaria; autoridades de salud; América Latina.

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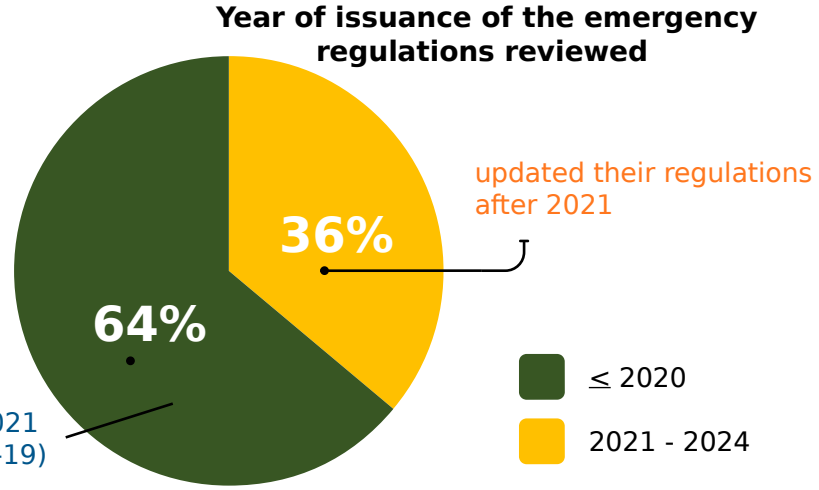
Methodology

- **Analysis of 22 countries in Latin America and the English-speaking Caribbean**
- **Evaluation period:** August 2023 - August 2024
- **Variables analyzed:**
  - Regulation publication year
  - Established authorization mechanisms
  - Applied risk criteria
  - Availability of information on websites

Results

1. Emergency Regulations

- **64%** of countries did not introduce changes their regulations for emergency situations.
- **32%** of countries submitted new regulations



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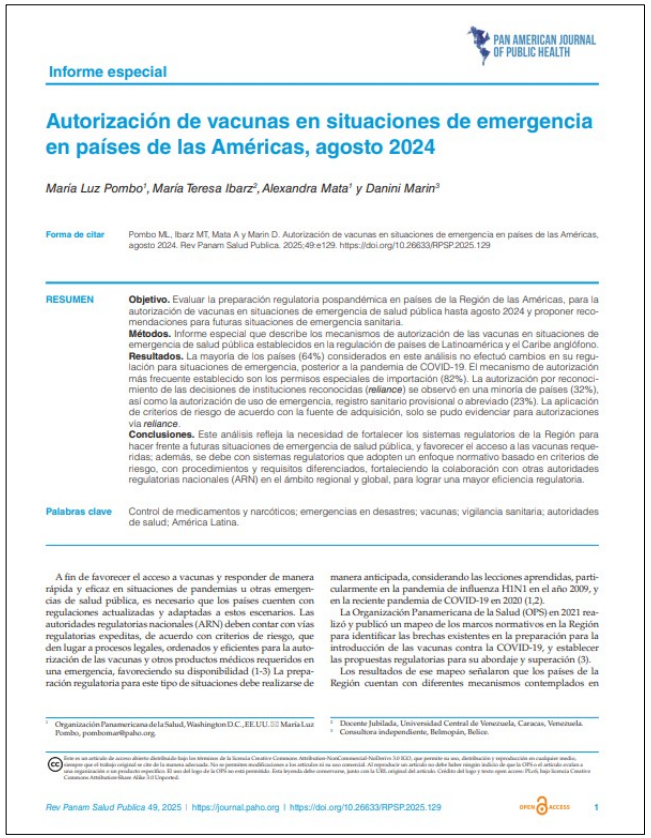

PAN AMERICAN JOURNAL OF PUBLIC HEALTH

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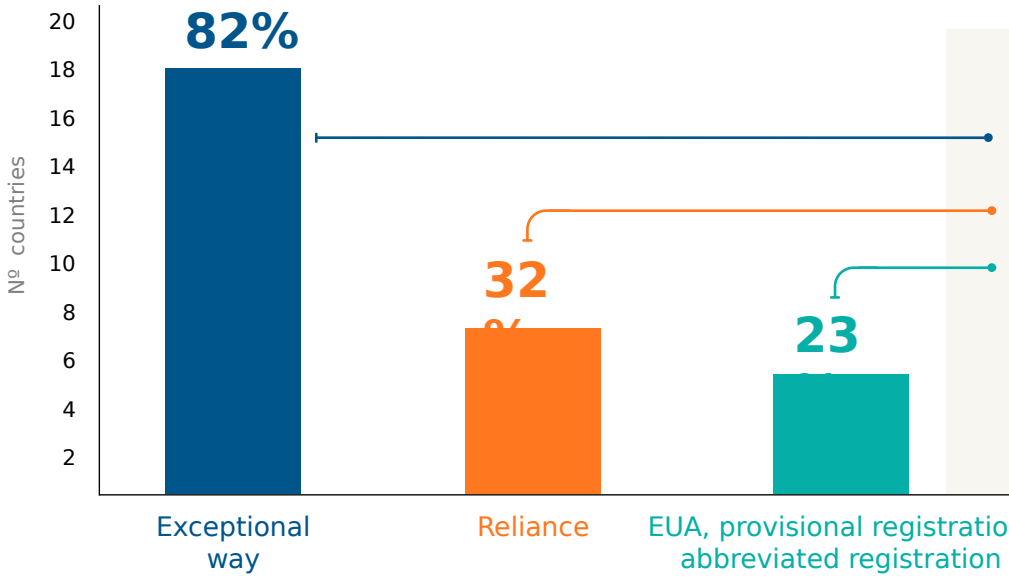
Results

- **2. Authorization Mechanisms**

Authorization mechanisms for medical products in emergency situations



The exceptional route (import permits) is the main authorization route 82%.

The reliance is applied in 32% of countries.

EUA, provisional/abbreviated registration in emergency situations, is applied in 23% of countries.

The only risk criterion applied was reliance

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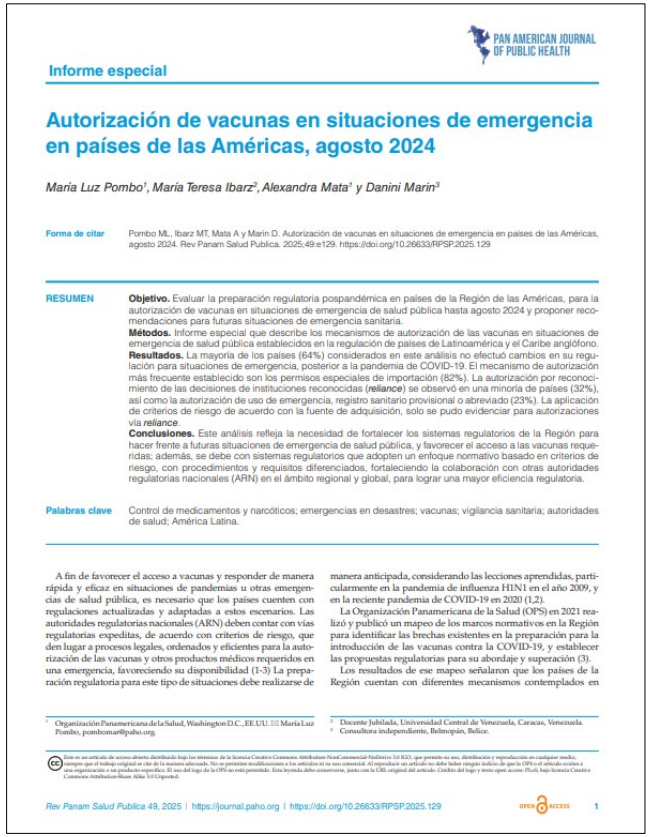

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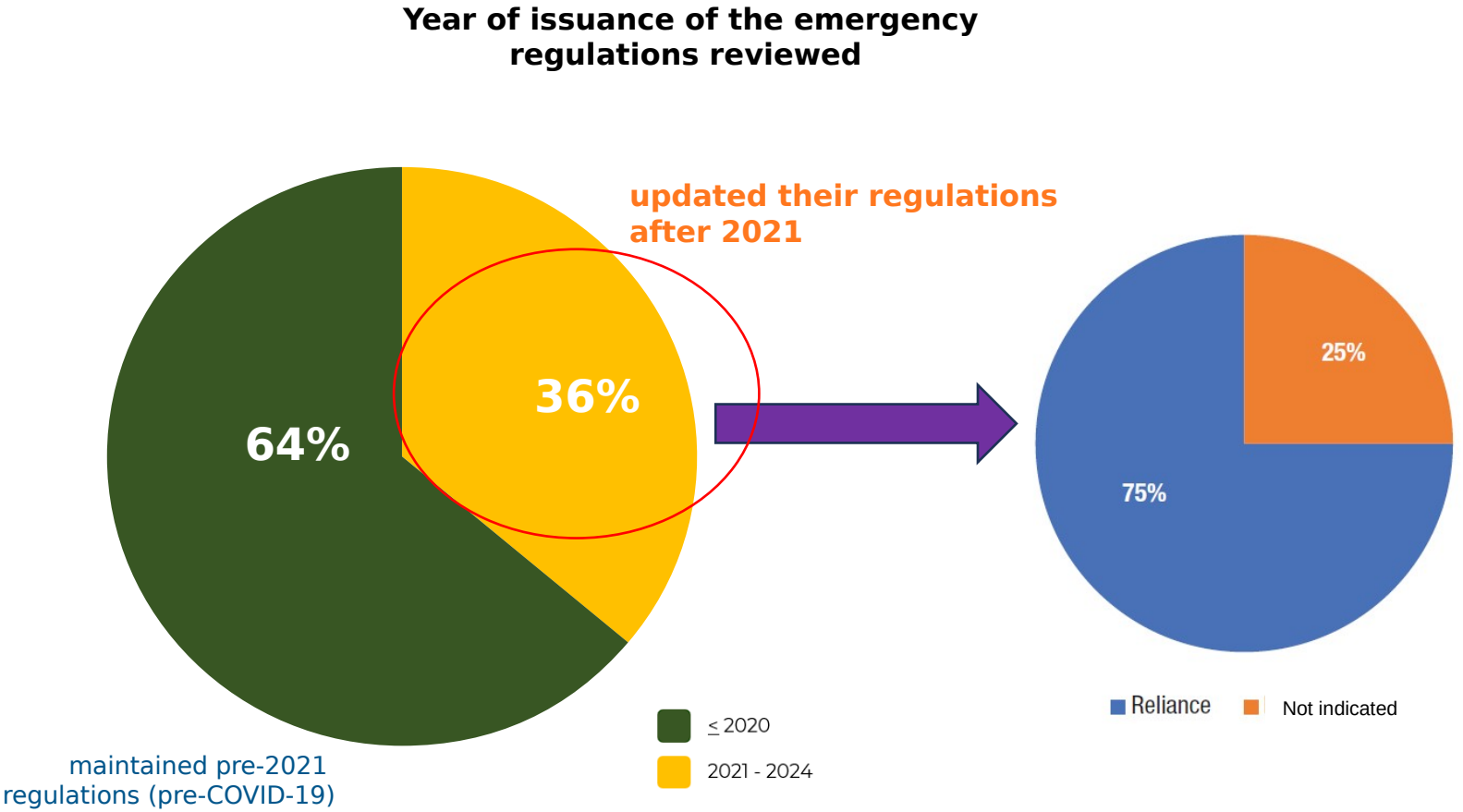

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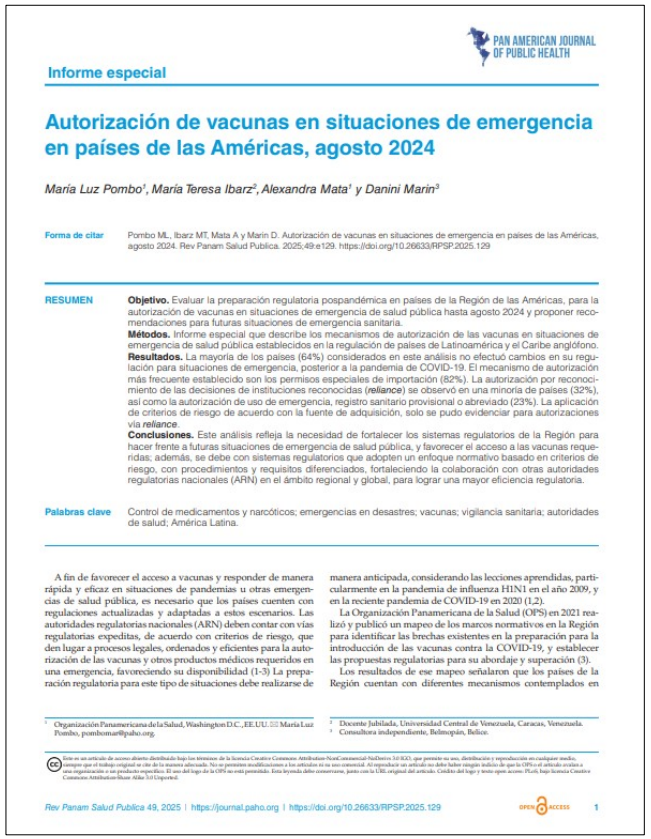

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Results

3. Other findings

Different acquisition pathways

Acquisition Pathways

- **Different acquisition routes involve different levels of risk, but the most commonly used authorization mechanism is** the exceptional route.

Transparency and Accessibility

- **None of the NRAs have specific sections on their websites about emergency procedures**
- **Lack of information about standards, requirements, and response times**

Limitations: This analysis is based on a review of the regulations received and the information available on the websites consulted.

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Authorization of vaccines and other medical products in emergency situations in the Region of the Americas

Key recommendations:

- **Review regulatory frameworks to include differentiated mechanisms based on risk criteria**
- **Establish simplified regulatory pathways for quality-assured products reliance**
- **Reduce the use of import authorizations without risk criterio**
- **Improve information on NRA websites**

Risk and probability criteria according to the source of acquisition

Proposed risk matrix

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Takeaways

Regulation

✓Prioritize regulatory preparedness for emergency situations.

Authorizations

✓**Producing countries:** prioritize emergency use authorization evaluations (EUA)

✓**Importing countries:**

- Rely on quality-assured procurement pathways (Reliance).
- Avoid using import permits without risk criteria.

International Cooperation

✓Maximize efficiency through collaboration among national regulatory authorities at regional and global levels.

Strengthening Regulatory Preparedness

Strengthening Regulatory Preparedness in the Americas: Lessons from COVID-19 and Emerging Expectations for Future Vaccine Authorization

Thank you

SESSION 2 · MODULE 3

Product-Specific & GMP Inspections

What makes RNA-vaccine facilities different — and where existing biologicals inspection checklists fall short.

A CEPI-led workshop for NRA regulators of the Americas

CEPI

THE PREMISE

Beyond the conventional biologicals checklist

RNA facilities introduce hazards and controls that traditional vaccine inspections were never designed to catch.

Different hazards

Ubiquitous RNases, organic solvents, ultra-cold storage — not the usual bioprocess risk set.

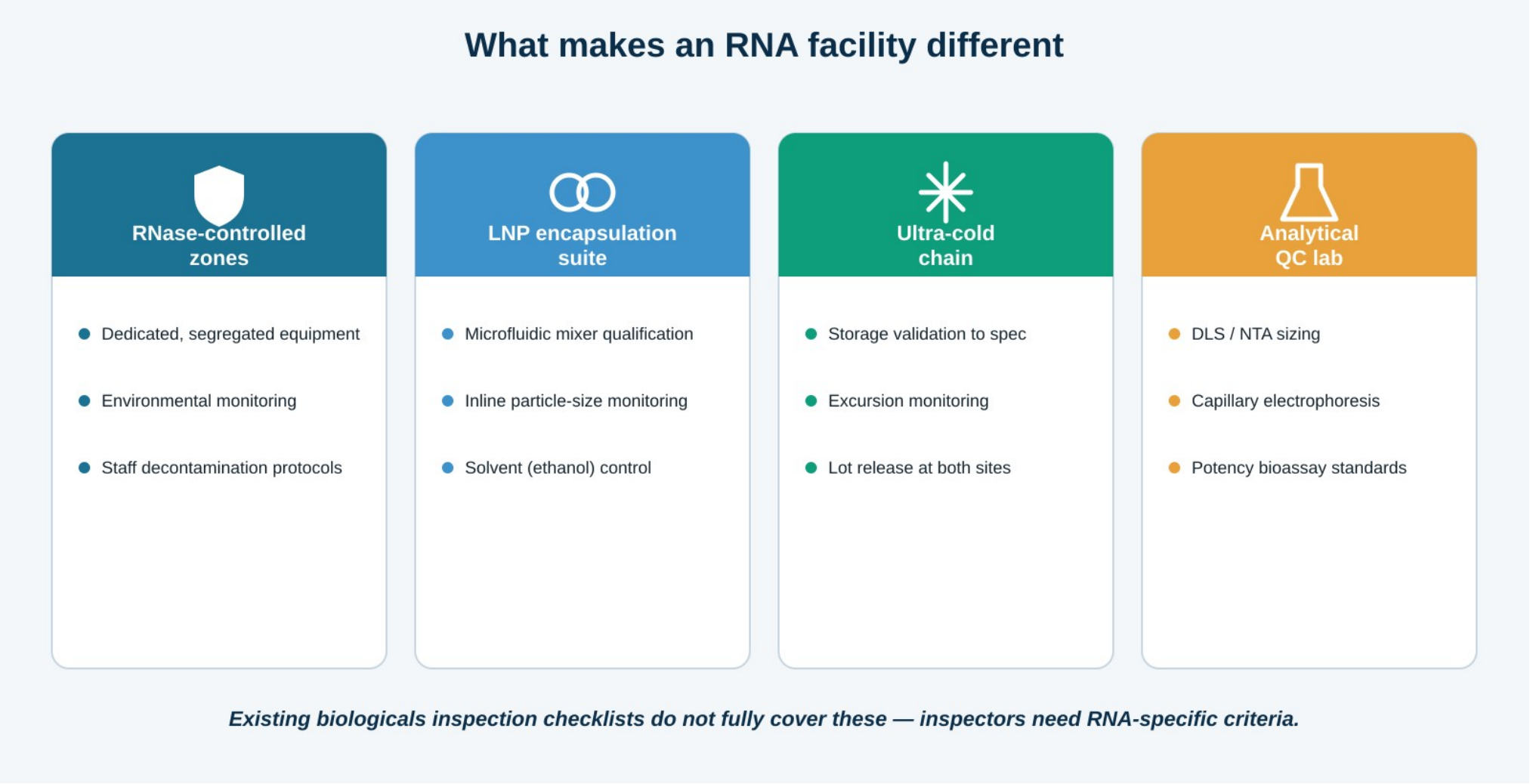
Different equipment

Microfluidic mixers and inline sizing instead of bioreactors and chromatography skids alone.

Different analytics

Nanoparticle sizing and RNA-integrity assays that many QC labs have not run before.

What makes an RNA facility different



Keeping the environment RNase-free

Why it dominates the design

RNases are everywhere — on skin, surfaces and equipment. A single contamination event can degrade a batch and destroy potency. RNase control is the organising principle of the facility.

Inspectors should verify it is designed in — not bolted on.

Segregated, dedicated equipment

Prevent cross-contamination; validated RNase-decontamination of surfaces and tools.

Environmental monitoring

Programme tuned to RNase and bioburden, not only classical particulates.

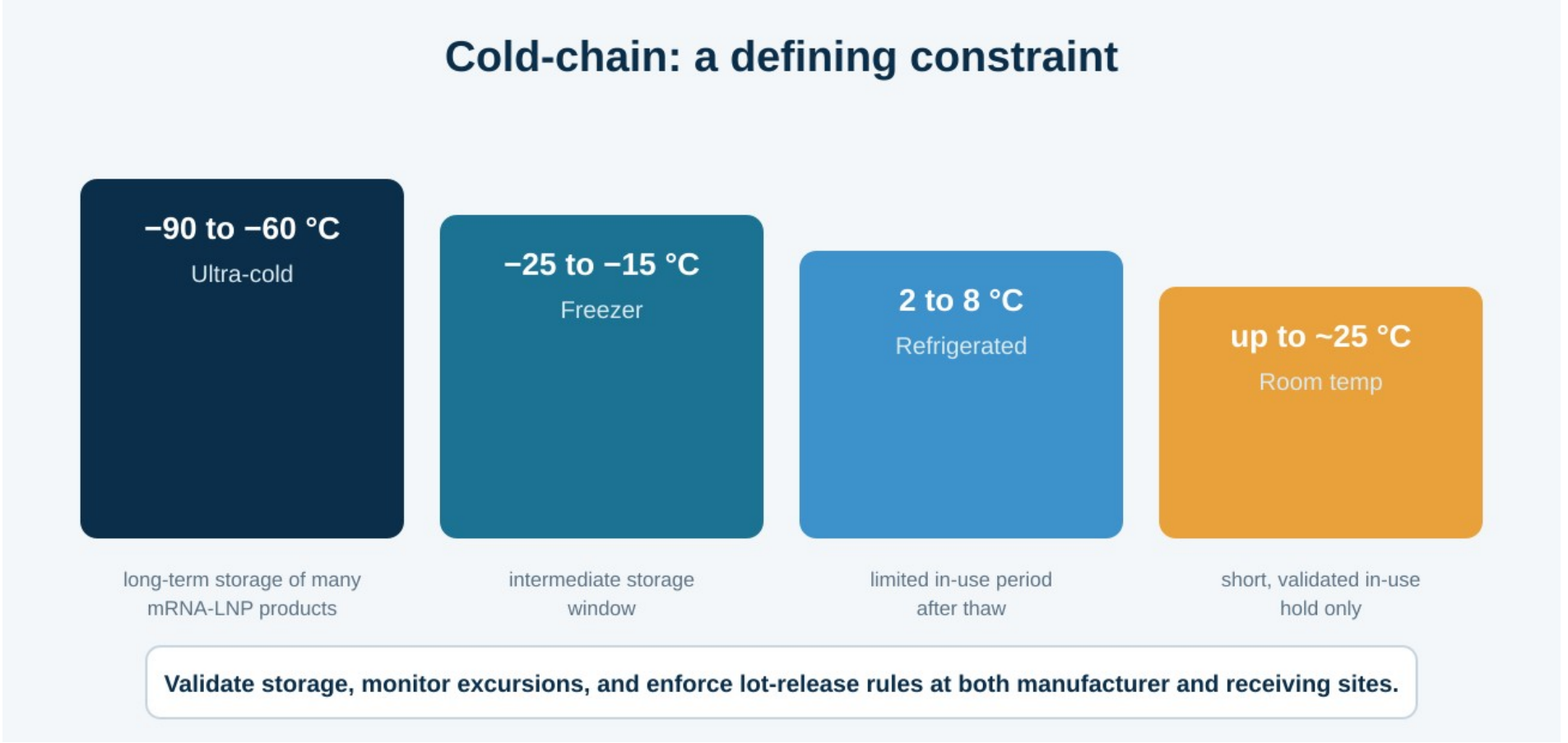
Staff decontamination protocols

Gowning, glove discipline and workflow that treat the operator as the main RNase source.

Material & water controls

RNase-free consumables and reagents; documented qualification of suppliers.

Ultra-cold storage and the release chain



Inspection focus: validated storage across the whole chain, continuous excursion monitoring, and lot-release rules honoured at both the manufacturer and every receiving site.

LNP ENCAPSULATION

Qualifying the encapsulation suite

Microfluidic mixer qualification

Flow rates, mixing ratio and shear are critical process parameters — qualify the equipment and its operating ranges, not just the output.

Inline particle-size monitoring

Real-time size and polydispersity control during formulation, with defined action limits.

Solvent (ethanol) control

Ethanol is a process-related impurity of particular relevance for LNPs — characterise and control its removal.

Encapsulation efficiency

Un-encapsulated mRNA is unstable; percentage encapsulation is a controlled critical quality attribute.

ANALYTICAL EQUIPMENT

Where existing checklists fall short

1

DLS / NTA

Dynamic light scattering & nanoparticle tracking for LNP size, distribution and zeta potential.

2

Capillary electrophoresis

RNA integrity, fragment sizing and %-intact transcript — orthogonal to chromatography.

3

Potency bioassays

Cell-based or cell-free expression assays with qualified reference standards.

4

Impurity & adduct analysis

IP-RP-HPLC / mass spectrometry for dsRNA, residual DNA and RNA-lipid adducts.

Reference-standard availability is often the binding constraint — potency and integrity assays are only as good as the standards behind them.

Mapping the gaps

Conventional checklist assumes…	RNA facility also needs…
Cell-culture bioprocess controls	**RNase-free design, dedicated equipment and staff decontamination**
Standard 2–8 °C cold storage	**Validated ultra-cold storage with continuous excursion monitoring**
Chromatography-based purity	**Nanoparticle sizing (DLS/NTA) and RNA-integrity by capillary electrophoresis**
Established potency reference standards	**New RNA potency/expression standards — often not yet available**
Familiar impurity panel	**dsRNA, residual DNA template, and RNA-lipid adduct control**

Findings at RNA facilities — the recurring themes

Across FDA and EMA inspections of mRNA-vaccine sites, the citable observations cluster into four themes.

Environmental & air control

Cleanroom HVAC and differential-pressure control in mRNA drug-substance suites — e.g., inadequate Grade C air handling.

Cleaning & contamination

Validated equipment cleaning before mRNA runs; RNase and cross-contamination discipline.

Segregation & materials

Defined, separate areas; control of expired or restricted materials used in mRNA production.

Cold chain & fill-finish

Ultra-cold storage and aseptic fill-finish; contamination and mold control at drug-product sites.

Cross-cutting: most public findings are conventional GMP issues at sites that also make mRNA — few are RNA-specific, and none are yet public for saRNA. But reliance already works: FDA accepted a Spanish (AEMPS) inspection, and EMA and Health Canada have inspected jointly.

Findings you can cite, by facility

Facility (role)	Agency · year	What was cited
Moderna — Norwood, MA *mRNA drug substance*	FDA Form 483 Sep 2023	Equipment not cleaned before mRNA-1273 drug-substance runs; expired / restricted materials in DS; Grade C cleanroom air handling inadequate.
Catalent — Bloomington, IN *fill-finish*	FDA Form 483 Sep 2022	Form 483 at Moderna bivalent fill-finish; site not initially added to the EUA pending FDA review.
Pfizer (ex-Hospira) — McPherson, KS *fill-finish*	FDA 483s (repeat)	Mold and microbial-contamination control, cleaning / disinfection — general aseptic issues, not RNA-specific.
Spikevax pharmacovigilance system *EMA + Health Canada — joint*	2021	5 major / 5 minor findings; CAPA endorsed — a joint-inspection and reliance example.
mNEXSPIKE — FDA Summary Basis for Regulatory Action *reliance record*	2025	FDA accepted a Spanish AEMPS facility inspection as ≈ VAI — a reliance example.

A Form 483 records an inspector's observations, not a final GMP determination. Sources: FDA 483s / EIRs (fda.gov, ORA Electronic Reading Room); EMA EPAR assessment reports; FDA Summary Basis for Regulatory Action.