
EU regulators' perspective
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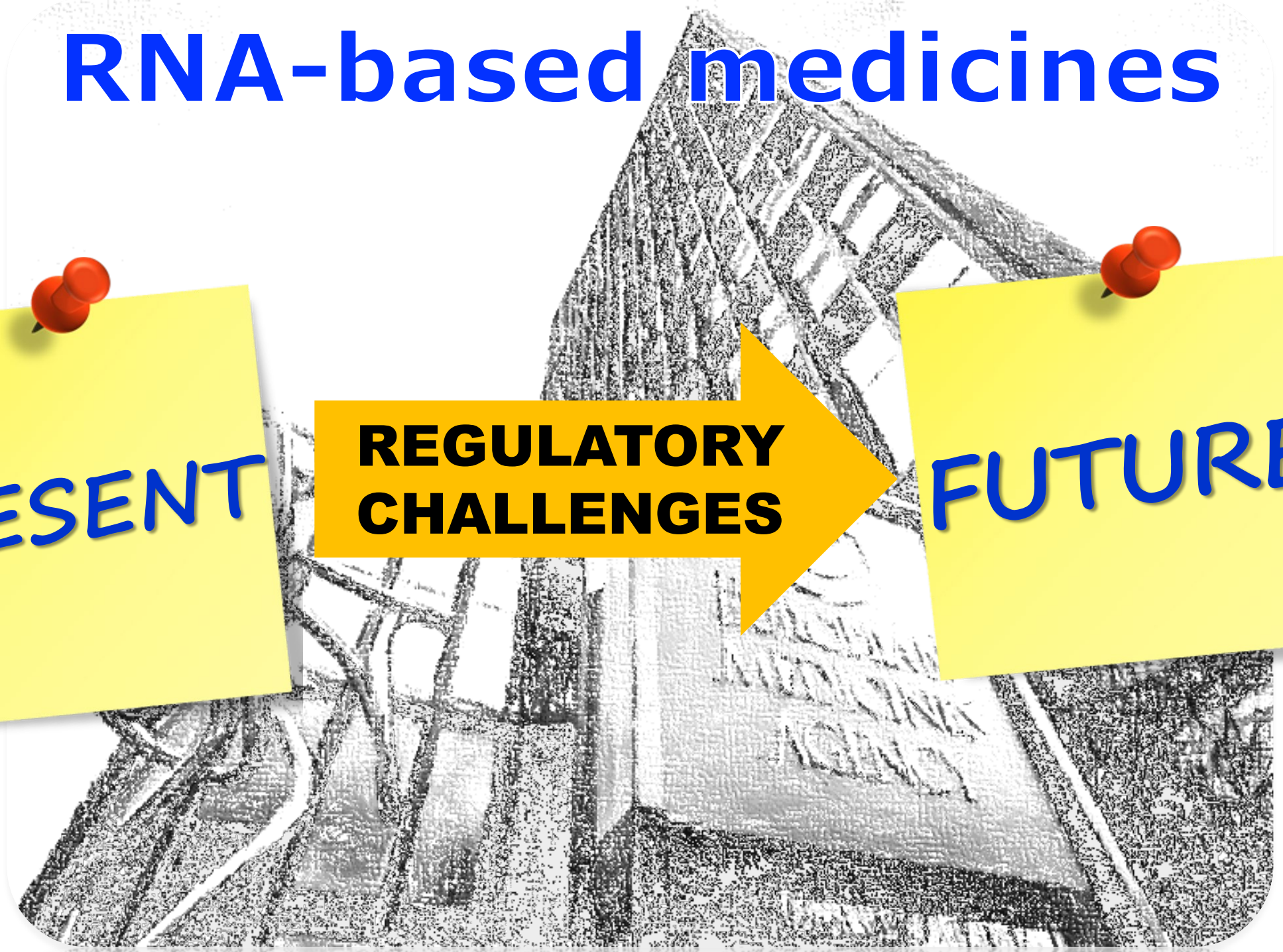
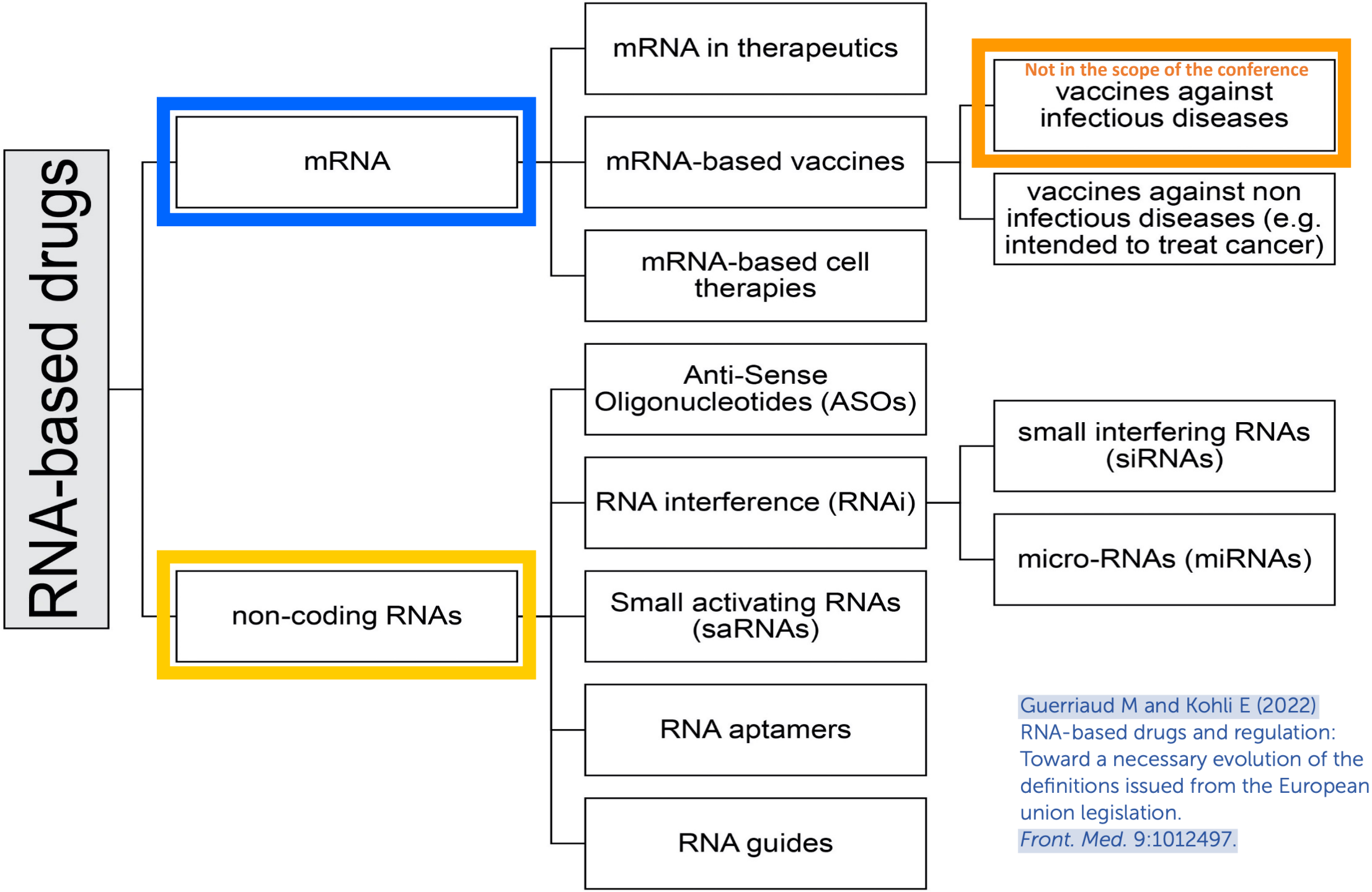
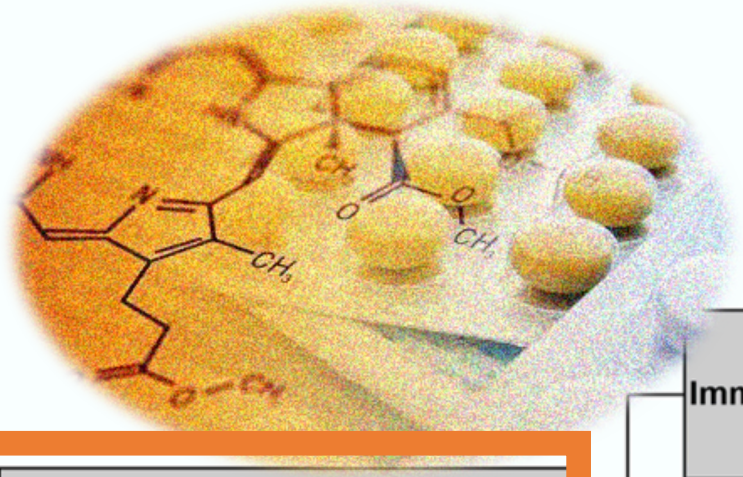
Sol Ruiz, PhD
Head of Biologics & ATMP (AEMPS)
Regulatory and scientific virtual conference on RNA-based medicines

RNA-based medicines



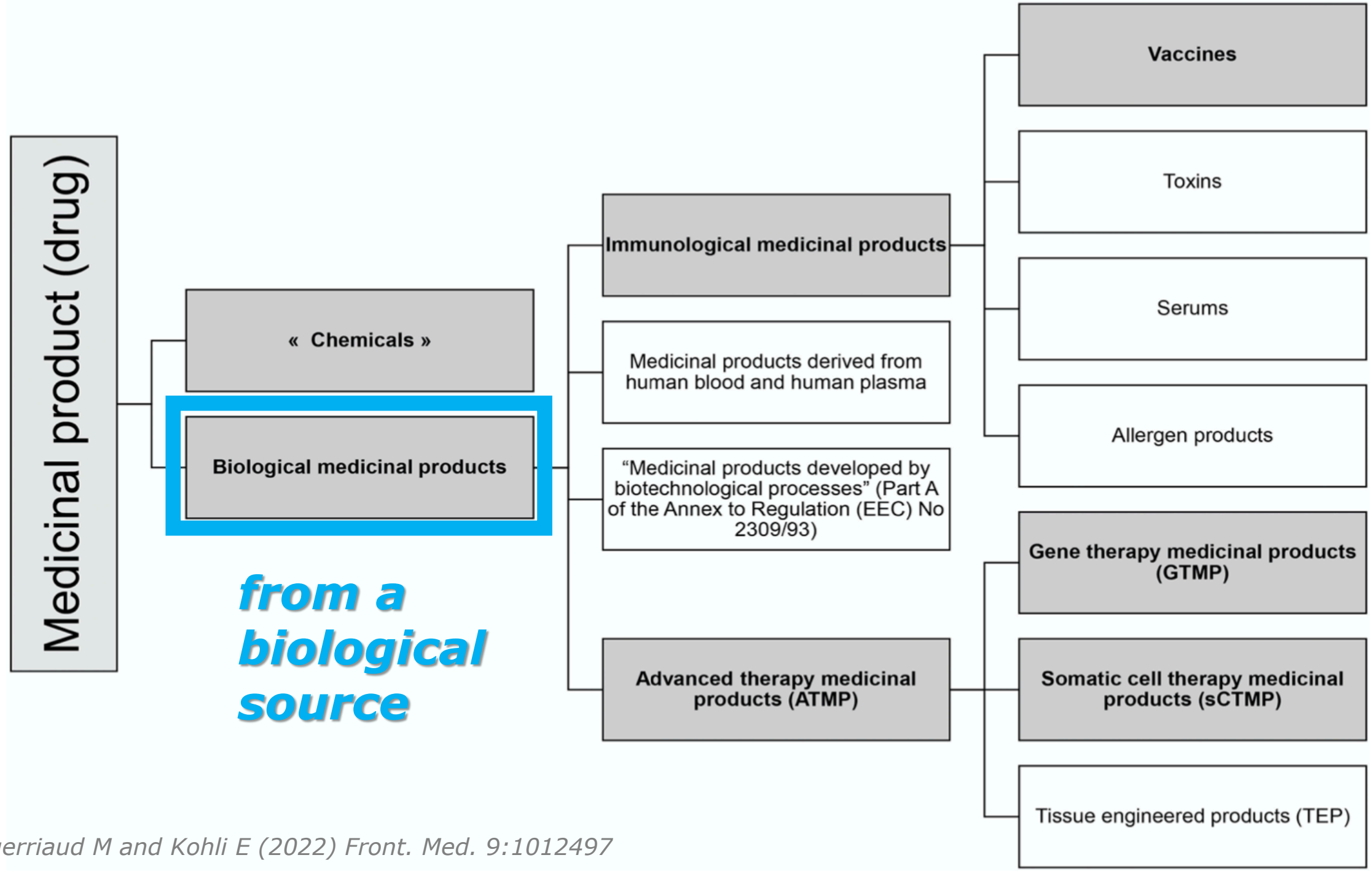


Guerriaud M and Kohli E (2022) RNA-based drugs and regulation: Toward a necessary evolution of the definitions issued from the European union legislation. *Front. Med.* 9:1012497.



- Medicinal product (drug)
  - « Chemicals »
  - Biological medicinal products
    - Immunological medicinal products
      - Vaccines
      - Toxins
      - Serums
      - Allergen products
    - Medicinal products derived from human blood and human plasma
    - “Medicinal products developed by biotechnological processes” (Part A of the Annex to Regulation (EEC) No 2309/93)
    - Advanced therapy medicinal products (ATMP)
      - Gene therapy medicinal products (GTMP)
      - Somatic cell therapy medicinal products (sCTMP)
      - Tissue engineered products (TEP)

Guerriaud M and Kohli E (2022) RNA-based drugs and regulation: Toward a necessary evolution of the definitions issued from the European union legislation. *Front. Med.* 9:1012497.



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Medicinal product (drug)

« Chemicals »

Biological medicinal products

from a biological source

Immunological medicinal products

Medicinal products derived from human blood and human plasma

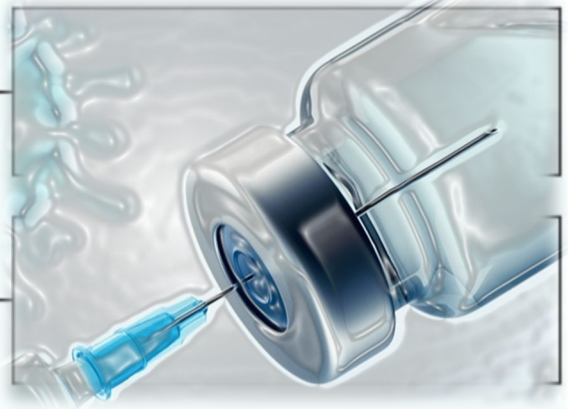
"Medicinal products developed by biotechnological processes" (Part A of the Annex to Regulation (EEC) No 2309/93)

Advanced therapy medicinal products (ATMP)

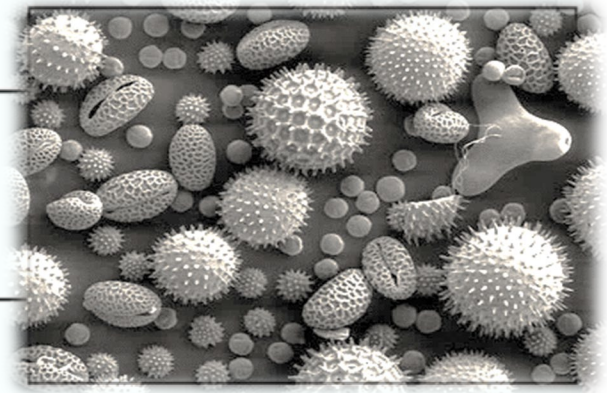
Gene therapy medicinal products (GTMP)

Somatic cell therapy medicinal products (sCTMP)

Tissue engineered products (TEP)



vaccines



allergens

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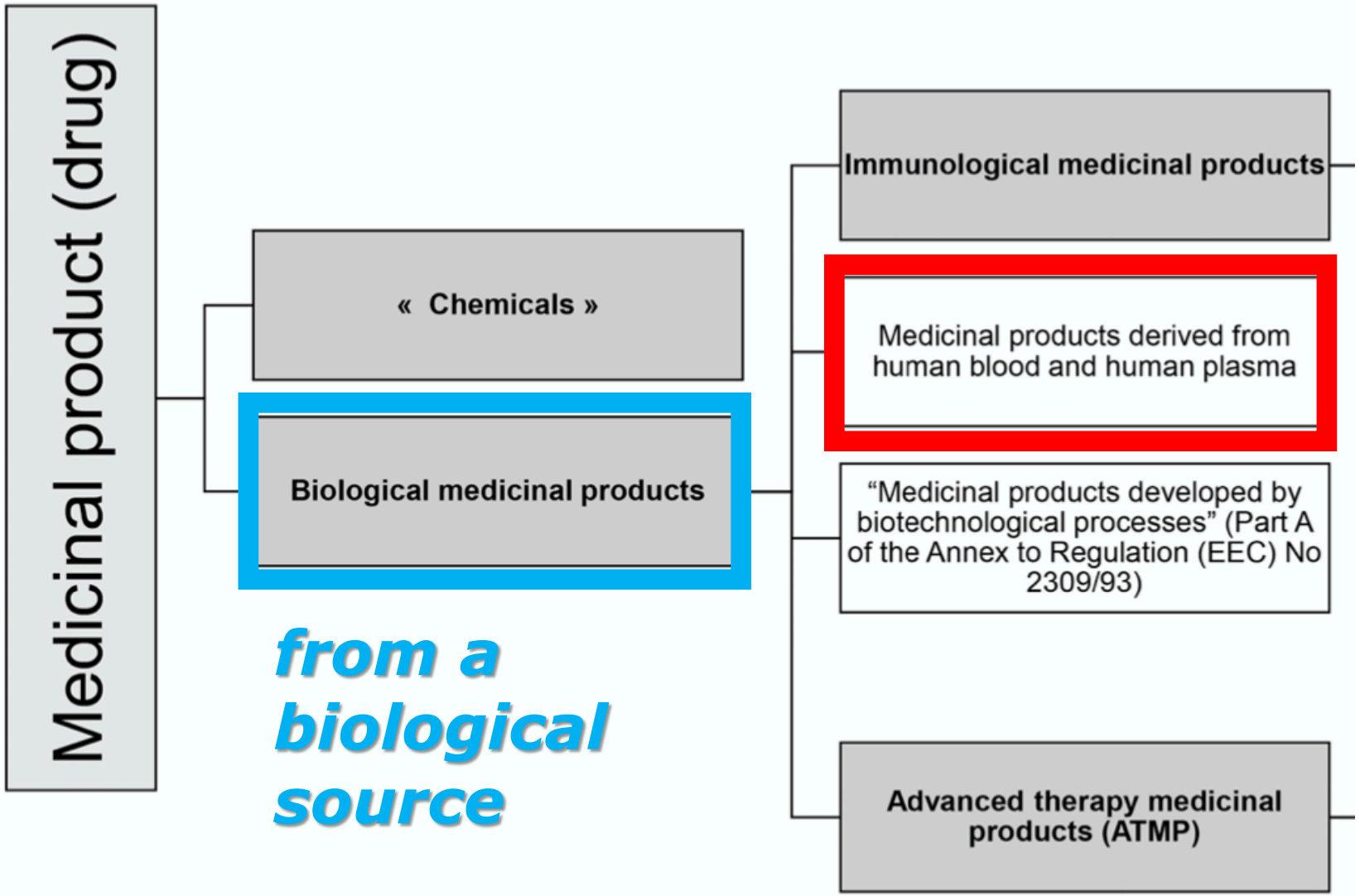

from a biological source

- **Coagulation factors**
- **Immunoglobulins**
- **Albumin**

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www.leinco.com/recombinant-proteins/

Medicinal product (drug)

« Chemicals »

Biological medicinal products

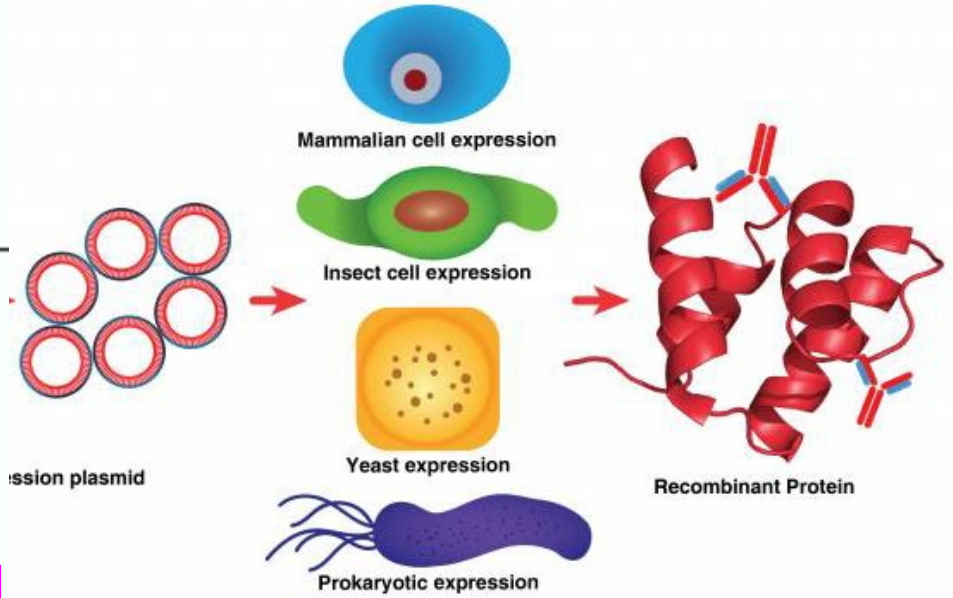
from a biological source

Immunological medicinal products

Medicinal products derived from human blood and human plasma

"Medicinal products developed by biotechnological processes" (Part A of the Annex to Regulation (EEC) No 2309/93)

Advanced therapy medicinal products (ATMP)



- **hormones**
- **enzymes**
- **monoclonal antibodies**
- **fusion proteins…**

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Medicinal product (drug)

« Chemicals »

Biological medicinal products

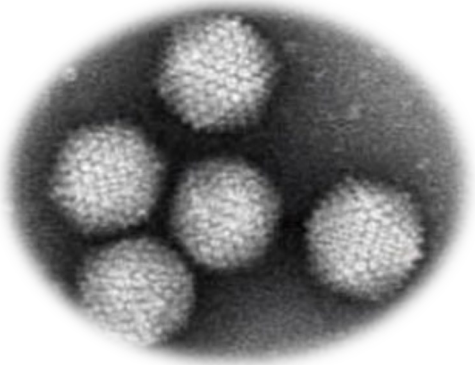
Immunological medicinal products

Medicinal products derived from human blood and human plasma

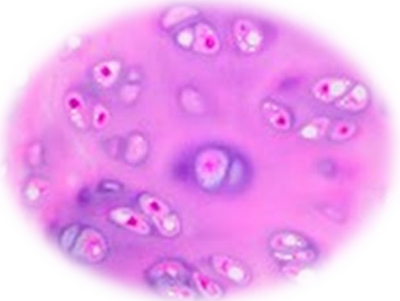
"Medicinal products developed by biotechnological processes" (Part A of the Annex to Regulation (EEC) No 2309/93)

Advanced therapy medicinal products (ATMP)

from a biological source



gene therapy



cell therapy

tissue engineering

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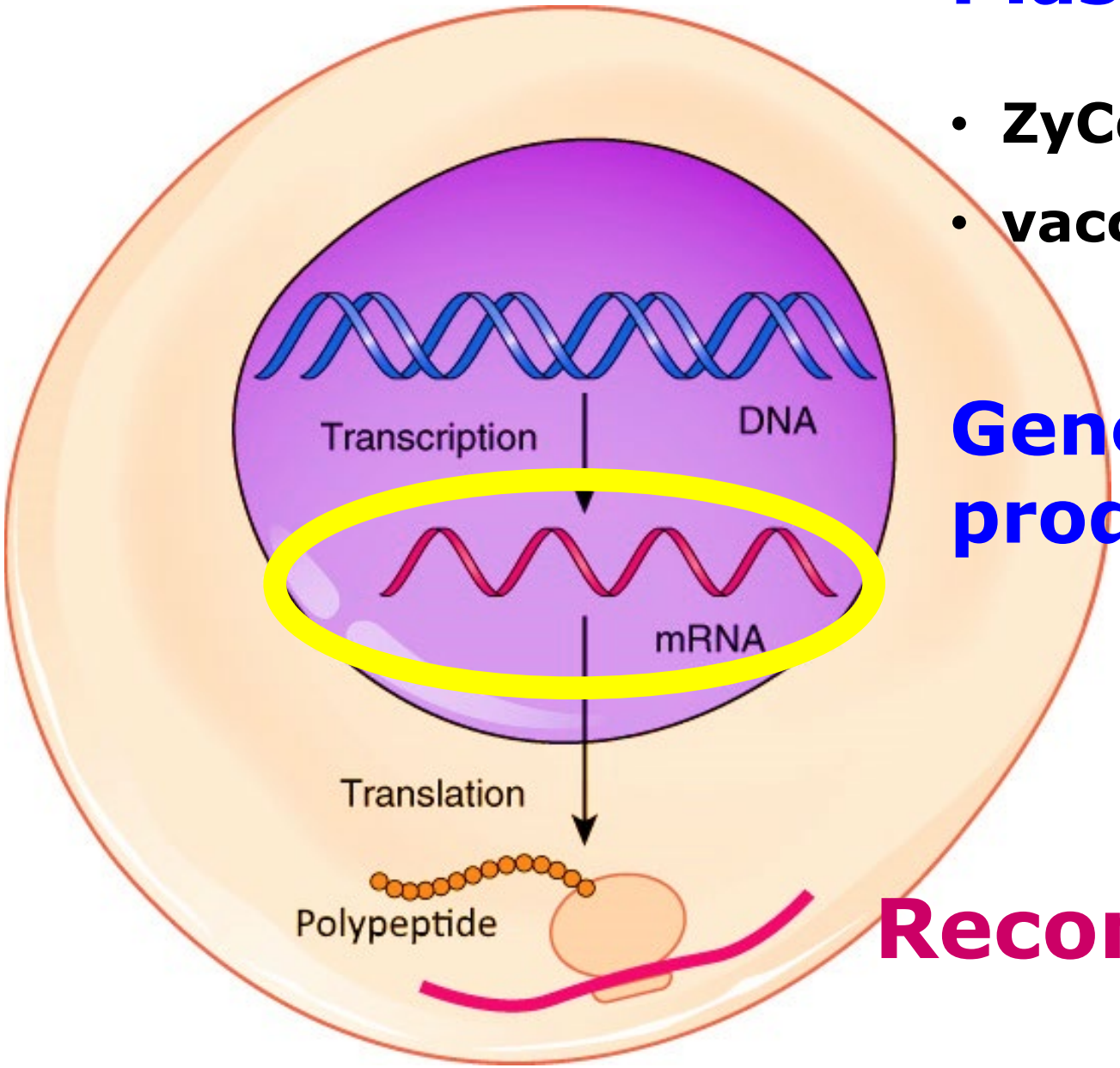
Plasmid DNA vaccines

- **ZyCoV-D (COVID-19, India)**
- **vaccines for veterinary use (EU, US)**



Gene therapy medicinal products

Recombinant proteins

humanbiology.pressbooks.tru.ca/chapter/5-4-rna/

A campaign to vaccinate people against COVID-19 in Goma, Democratic Republic of the Congo, in May.

SIX MONTHS, 1.7 BILLION DOSES: WHAT WE'VE LEARNT ABOUT COVID VACCINES

Monoclonal antibodies in the clinic

Despite initial teething problems, the number of clinically effective monoclonal antibodies is growing.

Janice M. Reichert

Monoclonal antibodies (mAbs) are nature's biological warheads, able to target and help eliminate foreign or abnormal agents from the body. In theory, replicating this powerful defense system could cure some of humanity's most deadly diseases. Indeed, when these biologics first entered clinical studies in the early 1980s they were heralded as "magic bullets" for the treatment of cancers, able to seek out and destroy tumor cells. However, early studies were disappointing and since then mAbs have fallen in and out of fashion. Today, 10 mAbs are now approved as therapeutics in the United States, so some of the original enthusiasm appears to have been justified. Here, a retrospective study provides a picture of the success of mAbs in the clinic, and prompts speculation about the most suitable choice of mAb class to pursue as a therapeutic.

Table 1. Success rates for mAbs entering clinical trials

Initiation of clinical trials (years)	Total number of mAbs	Number of mAbs discontinued	Number of mAbs approved	% completion[a]	% success [b]
1980–1982	2	1	1	100	50
1983–1985	9	8	0	89	0
1986–1988	33	29	2	94	6
1989–1991	34	29	2	91	6
1992–1994	41	23	5	68	18
1995–1997	33	12	0	36	0
1998–2000	34	2	0	6	0
All mAbs (1980–2000)	186	104	10	61	9
Murine mAbs	49	34	1	71	3
Chimeric mAbs	23	13	4	74	24
Humanized mAbs	59	15	5	34	25

[a] % completion = the percentage of products that have been discontinued and approved, providing an indication of how far trials have progressed. A low value will inevitably reduce the accuracy of the estimated success rates for that class of mAbs.
[b] % success = the percentage of mAbs that successfully completed trials and were approved by the US FDA.

The monoclonal revolution

The first generation of mAbs, unveiled in 1975 (ref. 1), were murine mAbs derived from mouse B-cell hybridomas (see "Monoclonal antibodies by design"). prone to HAMA reactions.

If mAbs were to become a class of successful therapeutics, then researchers needed to create nonimmunogenic mAbs with high binding affinities that could trig- the desired antibody, and few fully human mAbs entered clinical trials during the late 1980s.

Subsequent efforts concentrated on using genetic manipulation to produce

European public assessment reports (EPARs)

Output generated at: 25-01-2023

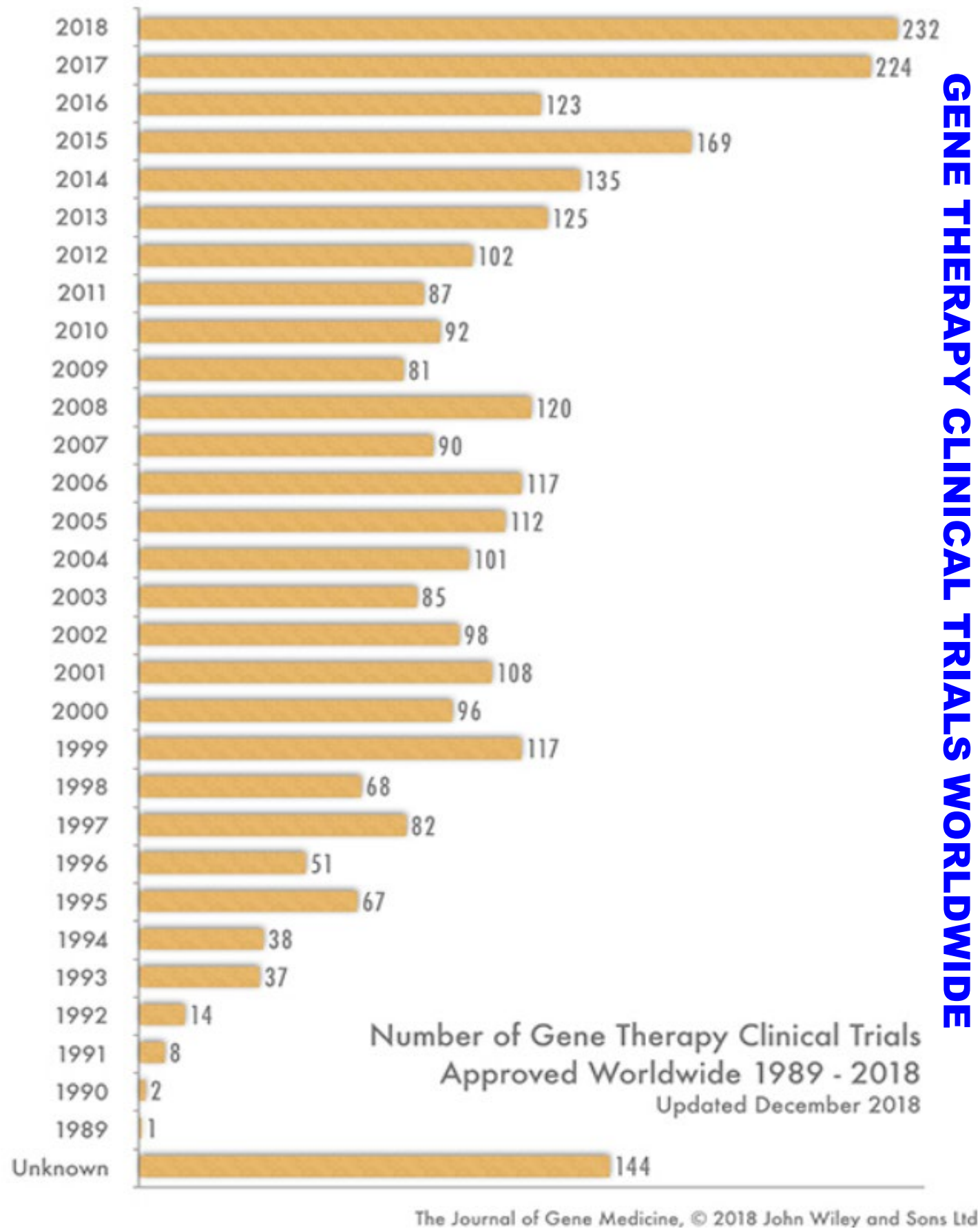
126 MAbs

36 biosimilar

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medicine name	Therapeutic area	International non-proprietary name (INN) common name
Repatha	Dyslipidemias; Hypercholesterolemia	evolocumab
Amgevita	Arthritis, Psoriatic; Colitis, Ulcerative; Arthritis, Juvenile Rheumatoid;	adalimumab
Stelara	Psoriasis; Arthritis, Psoriatic; Crohn Disease; Colitis, Ulcerative	ustekinumab
Praxbind	Hemorrhage	idarucizumab
Sarclisa	Multiple Myeloma	isatuximab
Benlysta	Lupus Erythematosus, Systemic	belimumab
Dupixent	Dermatitis, Atopic	dupilumab
Remsima	Arthritis, Psoriatic; Spondylitis, Ankylosing; Colitis, Ulcerative; Psoria	infliximab
Skyrizi	Psoriasis; Arthritis, Psoriatic	risankizumab
Kesimpta	Multiple Sclerosis, Relapsing-Remitting	ofatumumab
Hukyndra	Arthritis, Psoriatic; Arthritis, Juvenile Rheumatoid; Arthritis, Rheumat	adalimumab
Xevudy	COVID-19 virus infection	sotrovimab
Libmyris	Arthritis, Rheumatoid; Arthritis, Juvenile Rheumatoid; Spondylitis, An	adalimumab
Kyntheum	Psoriasis	brodalumab
Adakveo	Anemia, Sickle Cell	crizanlizumab
Lucentis	Wet Macular Degeneration; Macular Edema; Diabetes Complications	ranibizumab
Mvasi	Carcinoma, Renal Cell; Peritoneal Neoplasms; Ovarian Neoplasms;	bevacizumab
Onbevzi	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Fall	bevacizumab
Byooviz	Wet Macular Degeneration; Macular Edema; Diabetic Retinopathy; I	ranibizumab
Zirabev	Colorectal Neoplasms; Breast Neoplasms; Carcinoma, Non-Small-C	bevacizumab
Avastin	Carcinoma, Non-Small-Cell Lung; Breast Neoplasms; Ovarian Neopl	bevacizumab

GENE THERAPY CLINICAL TRIALS WORLDWIDE



12-2022

www.goal.com/en-bh/news/putellas-wins-uefa-women-champions-league-best-player/blt5a343deb0d17f28f

TABLE 1 Examples of RNA-based drugs currently or formerly on the market or under development.

Type of RNA	Subcategory (if applicable)	Drugs in the EU (green: approved/orange: withdrawn/yellow: under development)	Therapeutic indication	Regulatory status italics: probable status for MP under development)
mRNA	mRNA	UX053 NCT04990388 (3)	Glycogen Storage Disease Type III (GSD III)	*GTMP*
	mRNA-based vaccines	Comirnaty® tozinameran (1)	active immunization to prevent COVID-19	Vaccine
	mRNA-based vaccines for the treatment of cancer: direct injection of mRNA	IVAC MUTANOME® Phase I Clinical Trial NCT02035956 (4, 5)	advanced melanoma	*GTMP*
	mRNA-based vaccines for the treatment of cancer: mRNA cell therapies	autologous mature DCs co-electroporated with *in vitro* transcribed autologous renal cell RNA and CD40L RNA NCT00678119(6)	metastatic clear cell renal cell carcinoma	*sCTMP*
	mRNA based CAR-T cells produced *ex vivo*	Sparkcures Descartes-08 CAR-T cells NCT04816526 (7, 8)	high-risk multiple myeloma	*sCTMP*
	mRNA based CAR-T cells produced *in vivo*	Preclinical step. Proof of concept murine model (9)	cardiac fibrosis	*GTMP*
Antisense Oligonucleotides (ASOs)		Spinraza® nusinersen (19)	5q spinal muscular atrophy	"chemical"
		Tegsedi® inotersen (20)	stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis	"chemical"
		Waylivra® volanesorsen (21)	[. . .] genetically confirmed familial chylomicronemia syndrome (FCS) [. . .]	"chemical"
		***Withdrawn**: Kyndrisa® drisapersen* (69)	***was** expected to be used for the treatment of Duchenne muscular dystrophy*	"chemical"

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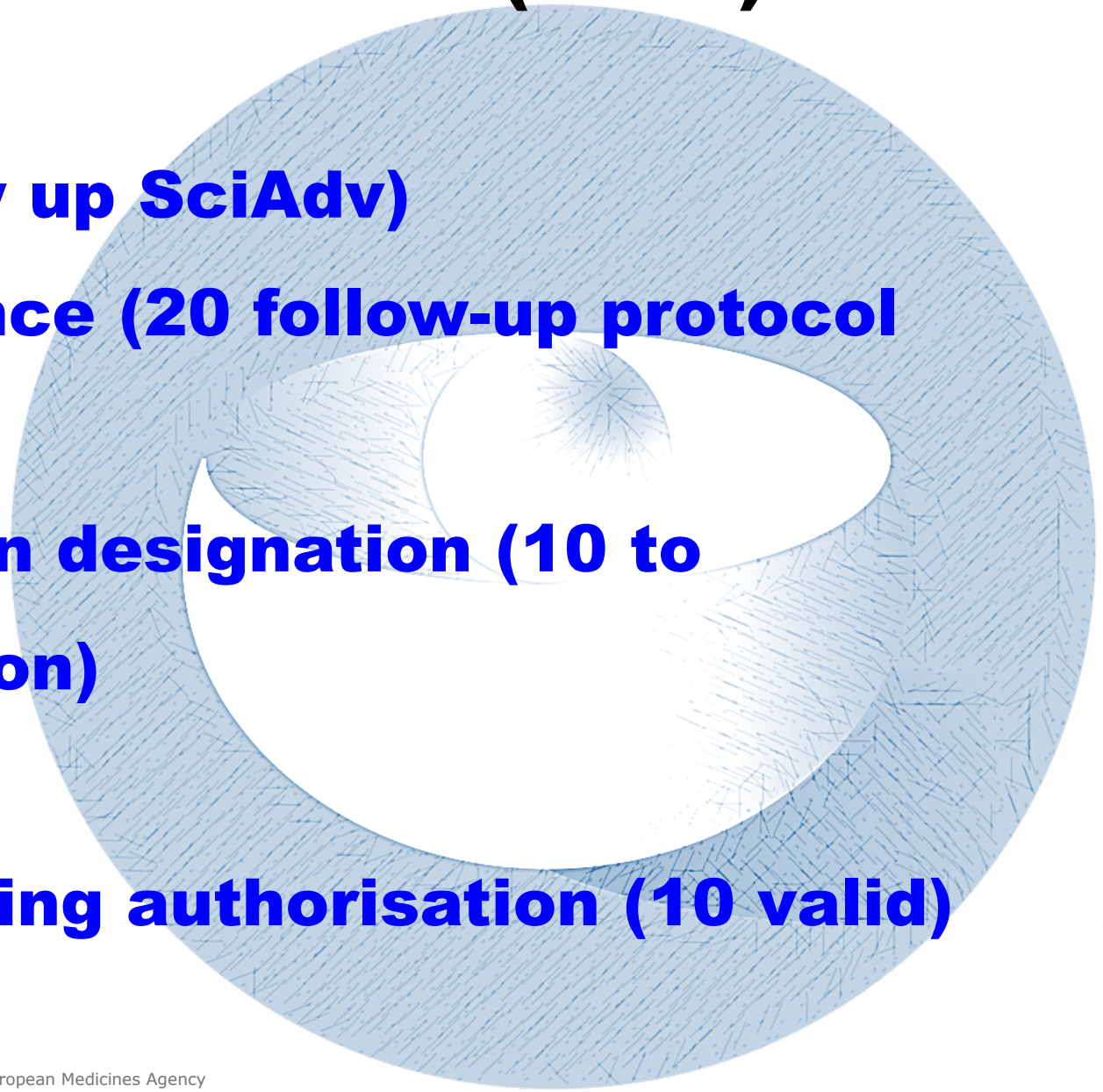
RNA interference (RNAi)	small interfering RNAs (siRNAs)	Onpattro® patisiran (22)	hereditary transthyretin-mediated amyloidosis (hATTR) in adults with stage 1 or stage 2 polyneuropathy	"chemical"
		Givlaari® givosiran (23)	acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older	"chemical"
		Oxlumo® lumasiran (24)	primary hyperoxaluria type 1 (PH1) in all age groups	"chemical"
		Leqvio® inclisiran (25)	primary hypercholesterolemia or mixed dyslipidemia in adults	"chemical"
	micro-RNAs (miRNAs)	Remlarsen (MRG 201) NCT03601052 (10, 11)	Keloid scar (target miR-29)	*"chemical"*
		Lademirsen (SAR339375/RG 012) NCT02855268 (12)	Alport syndrome (target miR-21)	*"chemical"*
RNA activation (RNAa)	small activating RNA (saRNA)	MTL-CEBPA (13) NCT05097911 (14) NCT04710641 (15)	advanced hepatocellular carcinoma (target CEBPA)	*"chemical"*
RNA aptamers		***Withdrawn:*** *Macugen® pegaptanib* (70)	***was indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults.***	"chemical"
RNA Guide/Direct genome editing*		NTLA-2001 (mRNA for Cas9 combined with a single short guide RNA) NCT04601051 (16, 17)	hereditary transthyretin amyloidosis	*GTMP*
		Nanoparticles formed by a cationic 4-armed polymer containing the gene editing components (CRISPR/Cas9 and the single guide RNAs) (18)	treatment of recessive dystrophic epidermolysis bullosa	*Biological MP*

*Drug status is determined by the associated nuclease.

RNA/antisense oligonucleotides (EMA):

- 95 initial SciAdv (10 follow up SciAdv)
- 50 initial protocol assistance (20 follow-up protocol assistance)
- 110 applications for orphan designation (10 to maintain orphan designation)
- 24 PIPs
- 13 applications for marketing authorisation (10 valid)



conclusions

- mRNA medicines well included in the current regulatory framework; definitions may need adaptation
- build from experience; specific guidance under development
- regulatory support available at any stage of development

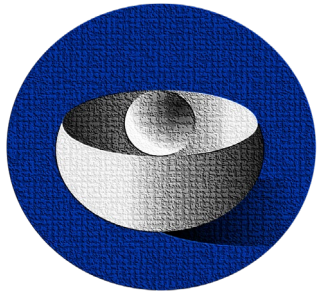
From laboratory to patient:

the journey of a medicine assessed by EMA

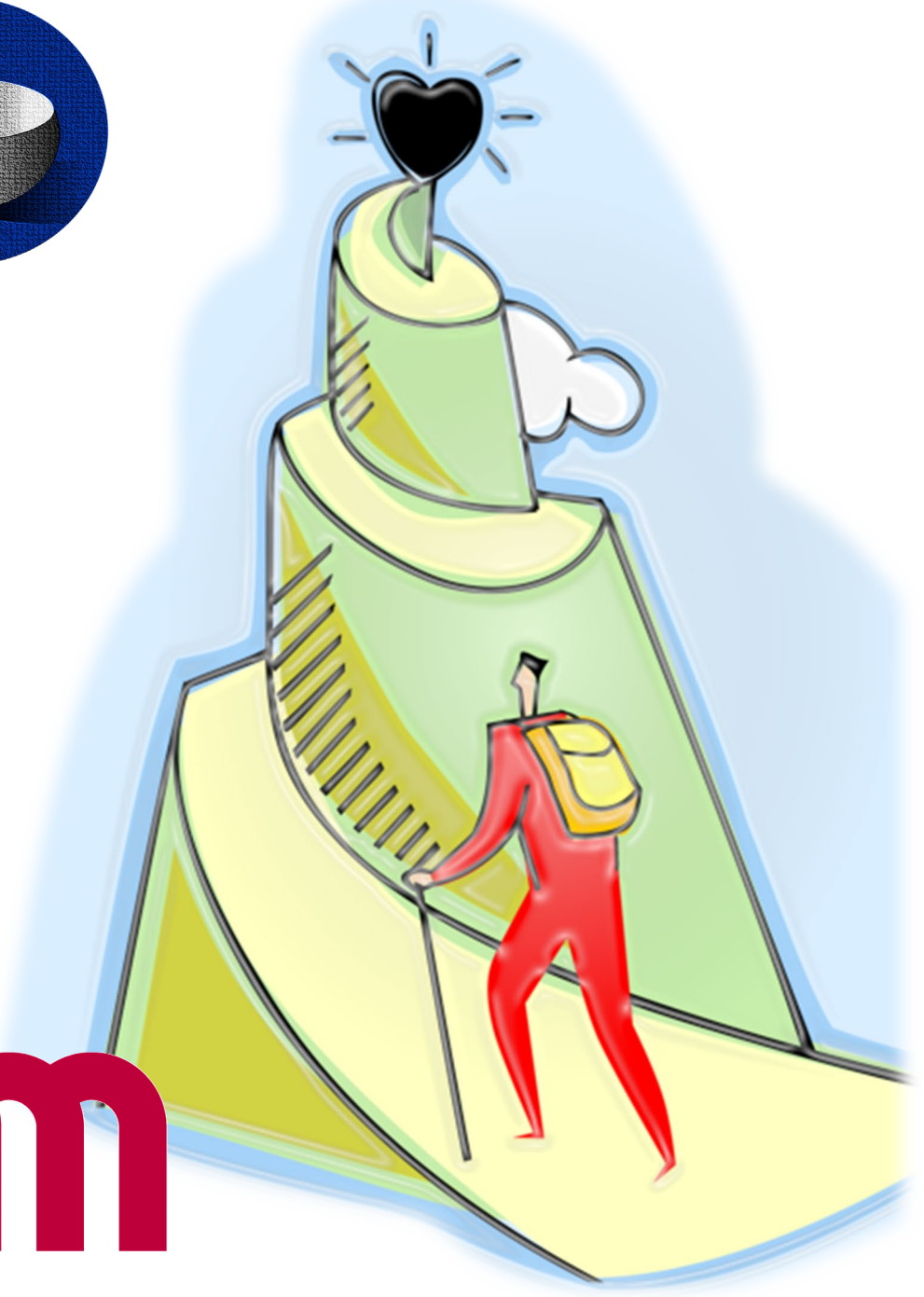
www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

What happens once a medicine is marketed

step 06



regulators advice can make a difference!!!



Initial research

step 01

cines Agency

Product classification: ATMP? Medicinal product?

SME?

Orphan indication?

Stage of product development? Future development?

Eligible for PRIME?

www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines

Adaptive pathways

Advanced therapies

Clinical trials

Compassionate use

Compliance

Data on medicines (ISO IDMP standards)

Ethical use of animals

Innovation in medicines

Innovation in medicines

Share

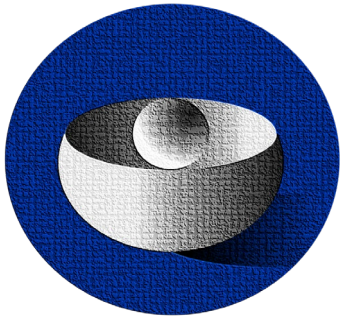


Table of contents

This content applies to human and veterinary medicines.

One of the European Medicines Agency's strategic goals is to foster research and the uptake of innovative methods in the development of medicines. This helps to make safe and effective innovative medicines available to patients in a timely manner.

www.ema.europa.eu/en/medicines

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Medicines under evaluation | National registers

EPAR

Search

For help on how to get the results you want, see our search tips.

Categories

- Human (10389)
- Veterinary (1275)
- Herbal (199)

Medicine name

- Select -

Active substance / international non-proprietary name (INN) / common name

- Select -

Medicine

- European public assessment reports (EPAR) (1981)
- Summaries of opinion (89)

11697 results

Sort by Medicine name

Human medicine European public assessment report (EPAR): Abasaglar (previously Abasria)

Insulin glargine, Diabetes Mellitus
Date of authorisation: 09/09/2014, Ⓑ , Revision: 12, Authorised, Last updated: 24/09/2021

Orphan designation: Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains (idecabtagene vicleucel) for: Treatment of multiple myeloma

Date of designation: 20/04/2017, Positive, Last updated: 03/12/2021

Human medicine European public assessment report (EPAR): Abecma

Idecabtagene vicleucel, Multiple Myeloma; Neoplasms; Cancer; Neoplasms, Plasma Cell; Hemostatic Disorders; Vascular Diseases; Cardiovascular Diseases; Paraproteinemias; Blood Protein Disorders; Hematologic Diseases; Hemic and Lymphatic Diseases; Hemorrhagic Disorders; Infectious Mononucleosis; Lymphoproliferative Disorders; Immunoproliferative Disorders; Immune System Diseases
Date of authorisation: 18/08/2021, ▼ , Ⓞ , Ⓒ , Revision: 5, Authorised, Last updated: 21/12/2022

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 107 NUMBER 3 | MARCH 2020

REVIEW

Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?

Tania Teixeira[1,*], Sandra L. Kweder[2] and Agnes Saint-Raymond[1]

There is talk of regulatory collaboration worldwide to protect public health and allow patients timely access to medicines. Here, we present the reality of the collaboration between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). This takes the form of near daily interactions, which may be less known outside of regulatory agencies. We present a review of what we call clusters, which involve the EMA, the FDA, and many other agencies under the umbrella of confidentiality arrangements. Through a survey of participants, we identified about 30 clusters of variable composition; these allow for the exchange of information and discussion among experts of applying regulatory science to common challenges in global drug development at every phase of

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 February 2021
EMA/73033/2021
International Affairs

Questions and Answers on the Pilot Project 'OPEN'

Opening our Procedures at EMA to Non-EU authorities

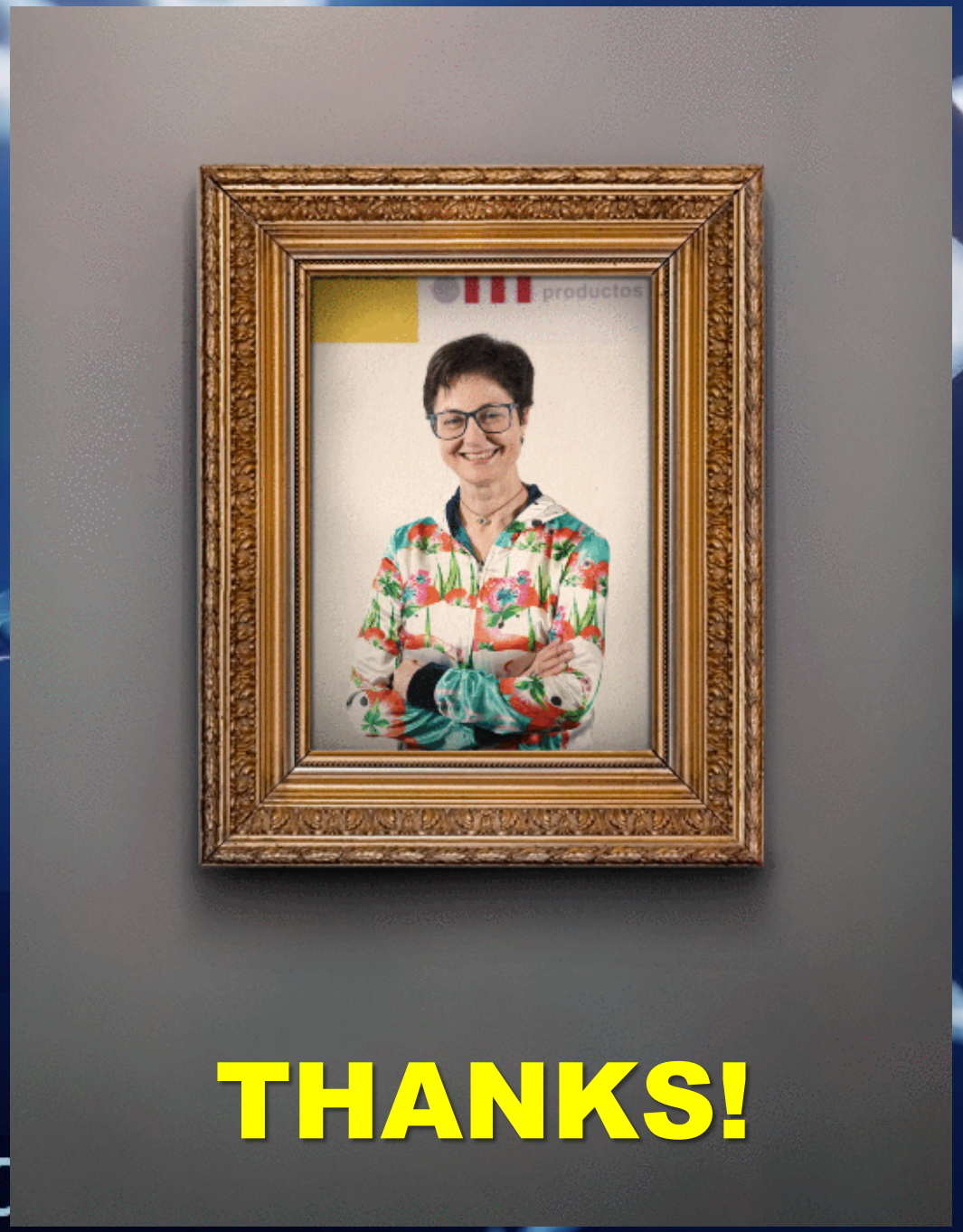
Questions and Answers on a pilot project regarding the participation of non-EU regulatory authorities in the Emergency Task Force (ETF) and the Committee for Human Medicinal Products (CHMP) assessment processes during the COVID-19 pandemic.

Introduction and Objectives

The COVID-19 pandemic is a global challenge for public health and requires the urgent development of new treatments and vaccines across the globe. International collaboration brings multiple benefits to regulatory authorities, and eventually to patients. Collaboration facilitates patient access through harmonisation or convergence, brings additional scientific expertise to a regulatory authority and simplification for pharmaceutical industry. It also increases overall transparency and can contribute to public trust because regulatory decisions are open to peer-review, either formal or informal.

The objective of the OPEN pilot project is to allow active international participation in our scientific evaluation, in the context of COVID-19 by regulatory authorities with confidentiality arrangements. This is in line with the principle of reliance and global regulatory good practices.

Regulatory and
conference on
RNA-based mec



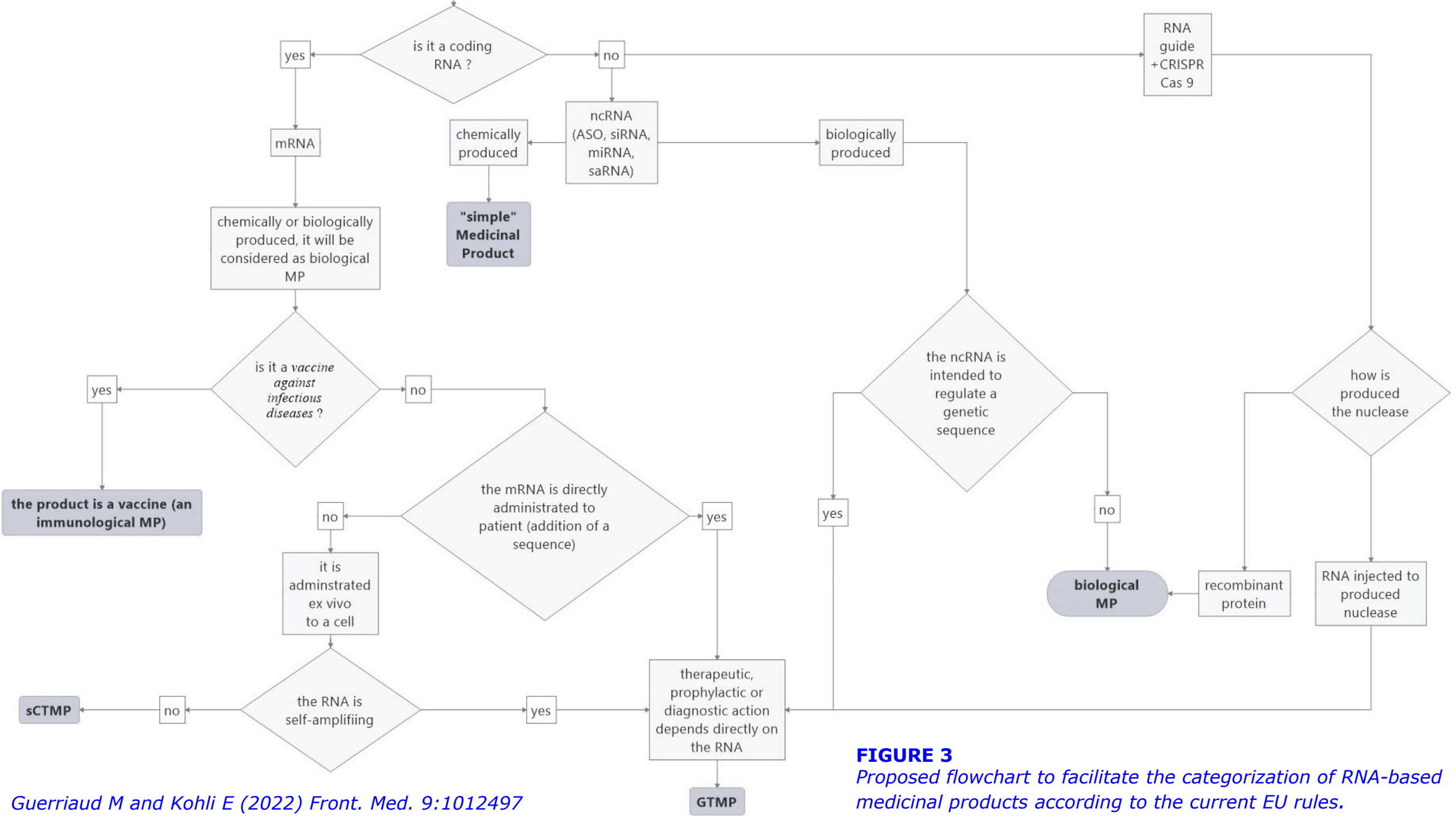


FIGURE 3
Proposed flowchart to facilitate the categorization of RNA-based medicinal products according to the current EU rules.

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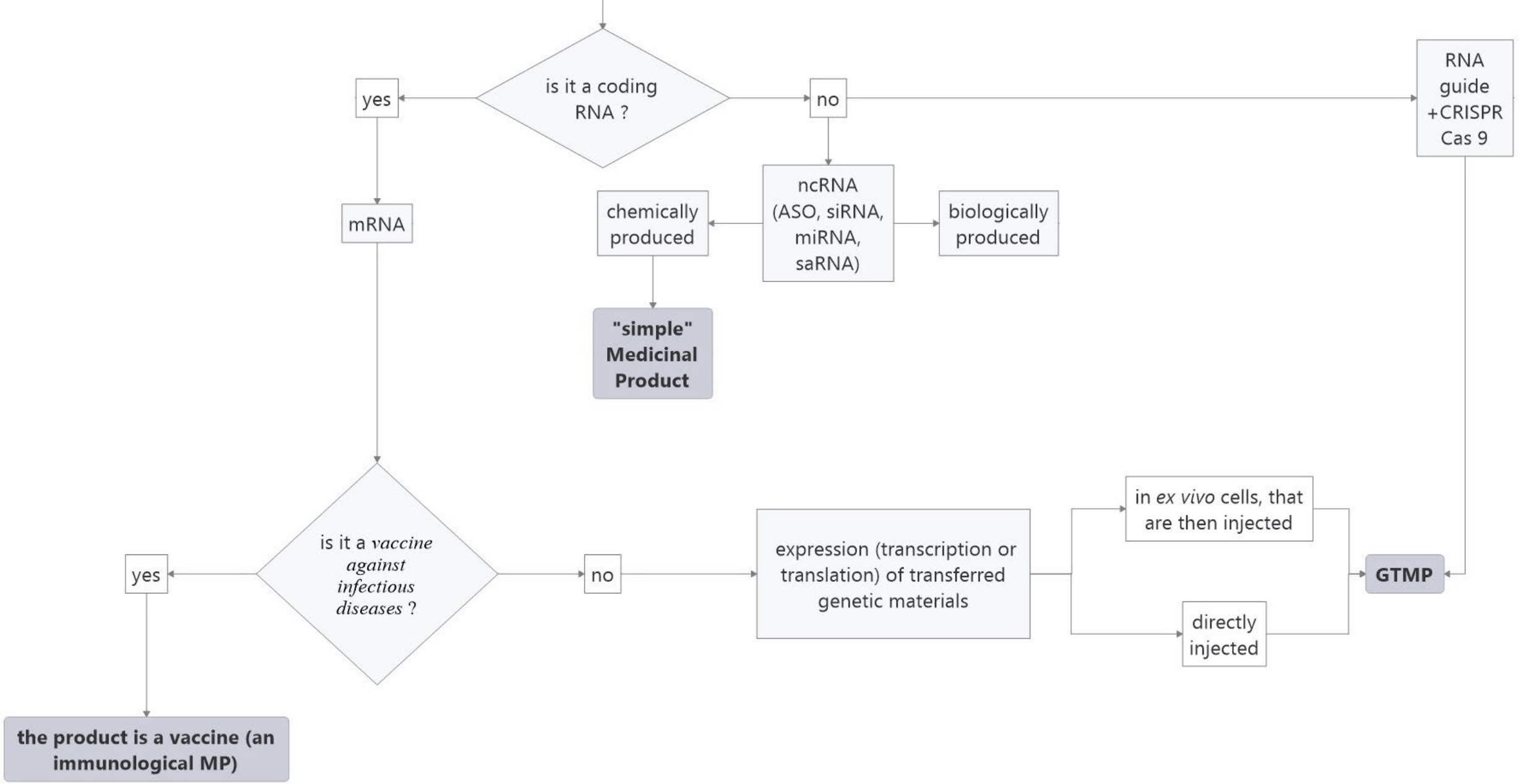

we hypothesize that the exclusion rule for vaccines against infectious diseases will be maintained if the ICH guideline is integrated into the EU regulation

FIGURE 4
Proposed flowchart to facilitate the categorization of RNA-based medicinal products according to the ICH rules project.