Feature » BMJ Investigation

Is the US's Vaccine Adverse Event Reporting System broken?

BMJ 2023 ; 383 doi: https://doi.org/10.1136/bmj.p2582 (Published 10 November 2023)
Cite this as: *BMJ* 2023;383:p2582

Jennifer Block, investigations reporter

Author affiliations

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A BMJ investigation has raised concerns that the VAERS system isn't operating as intended and that signals are being missed. **Jennifer Block** reports

Three weeks after receiving a second dose of a covid vaccine, Robert Sullivan collapsed at home on his treadmill. An anaesthesiologist in Maryland, USA, he was a particularly fit 49 year old: the week before falling ill, he'd been happily skiing at altitude in Colorado.

https://www.bmj.com/content/383/bmj.p2582

VI CHAPTER
REGISTRATION OF COMMPLICATIONS AFTER SGEI AND PROVISION OF INFORMATION ON IT

23. Subvaccination or vaccination-specific immunoglobulin and sera are registered with NVSC.

24. Doctor diagnosed with complications after vaccines (excl. When complications are diagnosed after vaccination with COVID-19 disease vaccine), complete the Adverse Vaccine Reposure Investigation Protocol (Annex 4 to the description) and within 15 calendar days of the complication after the detection of the syllable (if the complication after the syllable caused life or death, – per 1 calendar day) sends in writing (E. delivery system or in another safe manner) to the NVSC.

Wect changes:

No. V-1140, 2023-11-03, published in TAR 2023-11-03, i. k. 2023-21485

25. In the event of non-preventability in the completion of the vaccination study protocol, the CISSC collects additional information in the event of a suspicion of potentially associated post-vaccine complications and clarifies the study protocol for adverse reactions to vaccines. NVSC provides ULSVIS data for the study protocol for adverse reactions to vaccinations within 5 working days (if the complication after the syllable caused life or death – within 1 working day) from the study of adverse reactions to vaccines receipt or adjustment of the protocol.

Batch dependency
Vibeke Maniche

Analysis of adverse event variation between Pfizer COVID-19 vaccine batches doesn't indicate safety problems, contrary to claim by John Campbell

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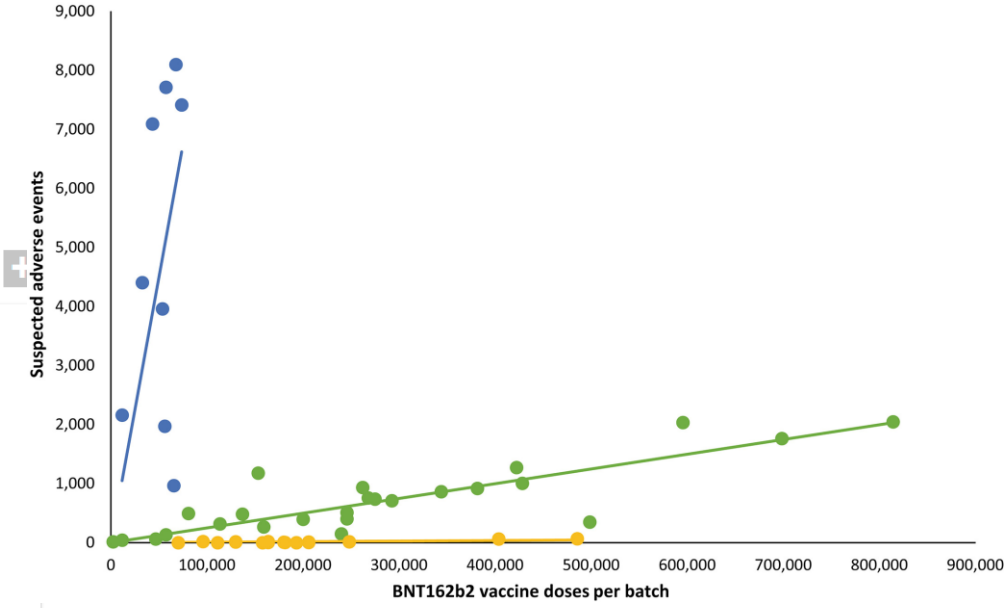
CLAIM

Danish researchers show high rates of side effects from Pfizer COVID-19 vaccine, indicating problems with safety

VERDICT

MISLEADING

SOURCE: John Campbell, Vibeke Manniche, YouTube, 5 Jul 2022



https://healthfeedback.org/claimreview/analysis-adverse-event-variation-pfizer-covid-19-vaccine-batches-doesnt-indicate-safety-problems-contrary-john-campbell/

SARS-CoV-2 Infection COVID-19	Biological: BNT162b1 Biological: BNT162b2 Other: Placebo	P P

Study Design

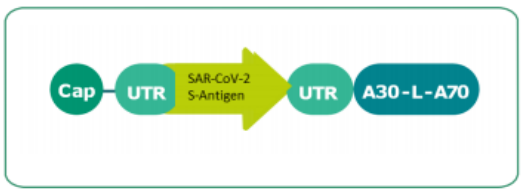
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	43998 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Prevention
Official Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAF EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS
Actual Study Start Date :	April 29, 2020
Estimated Primary Completion Date :	August 1, 2021
Estimated Study Completion Date :	January 29, 2023

Arms and Interventions

Arm	Intervention/treatment
Experimental: Low dose, 18-55 years of age (2 doses)	Biological: BNT162b1 Intramuscular injection Biological: BNT162b2 Intramuscular injection
Experimental: Low-mid dose, 18-55 years of age (2 doses)	Biological: BNT162b1 Intramuscular injection

BNT162 mRNA vaccine technologies

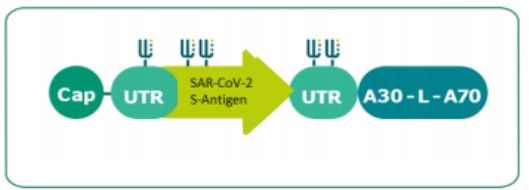
Uridine mRNA (uRNA)[1]



Rationale

- Prime / boost
- Strong adjuvant effect
- Active at low doses
- Strong antibody response
- CD8 T-Cells > CD4 T-Cells

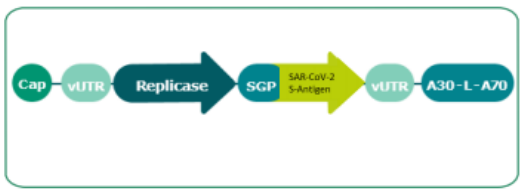
Nucleoside-modified mRNA (modRNA) [2]



Rationale

- Prime / boost
- Moderate adjuvant effect
- Very strong antibody response
- CD4 T-Cells > CD8 T-Cells

Self-amplifying mRNA (saRNA) [3]



Rationale

- Prime (1x injection)
- Long-term activity
- Very strong antibody response
- Very strong T-Cell response (CD8 and CD4)
- Potent immune protection at low doses (approx. 60x lower dosages required to induce immunity vs. uRNA observed in preclinical models)

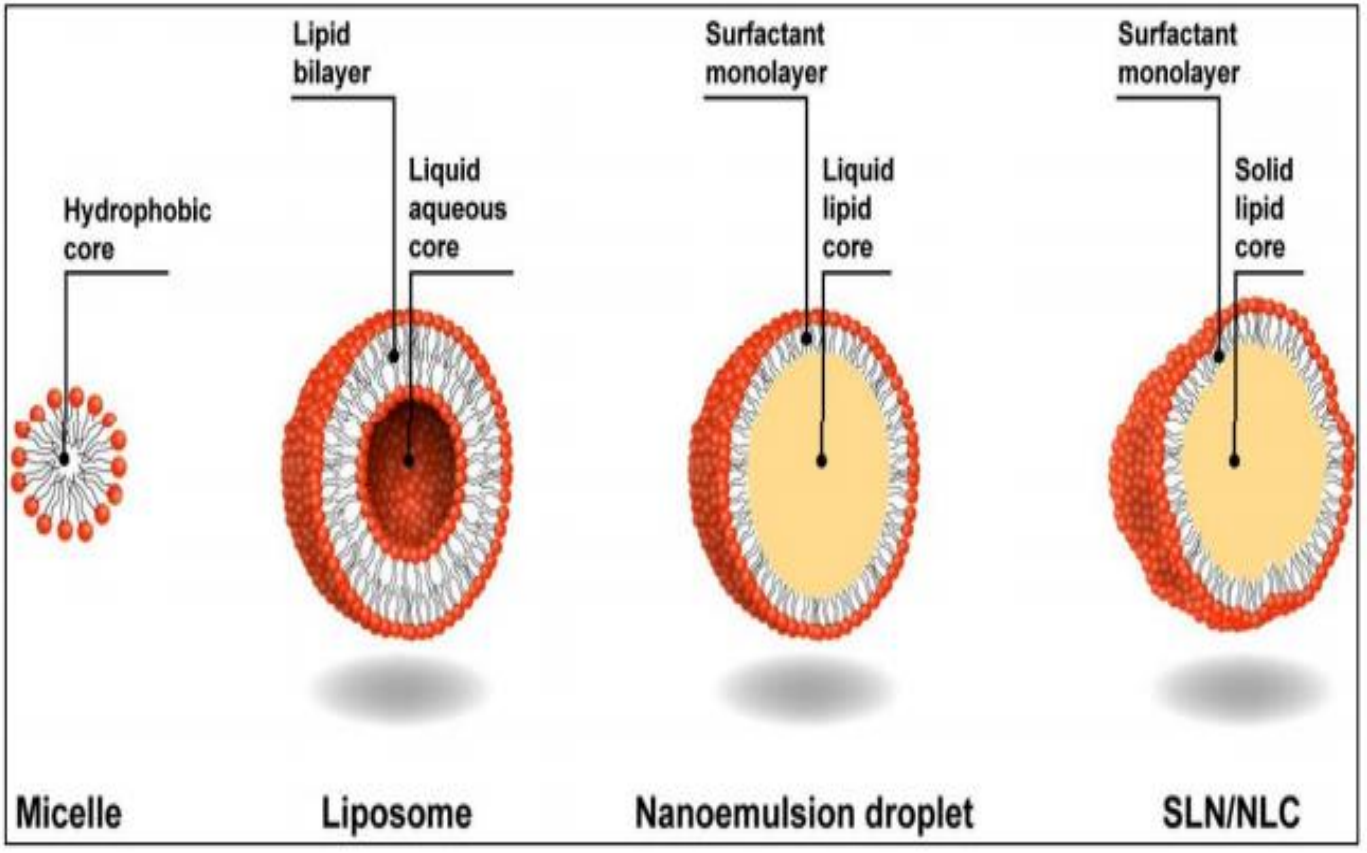


Fig 1: Comparison between micelles, liposomes, nanoemulsions and solid lipid nanoparticles. (Micelles with hydrophobic core which is formed by the tails of the surfactant molecules. Liposomes with aqueous core surrounded by a double phospholipid layer. Nanoemulsions droplets with hydrophobic liquid core composed of the oil that is dispersed in the water and stabilized by a surfactant monolayer. SLN and NLC with hydrophobic core of solidified lipid; often the solidification/crystallization of the lipid results in non-spherical shape of the particles).

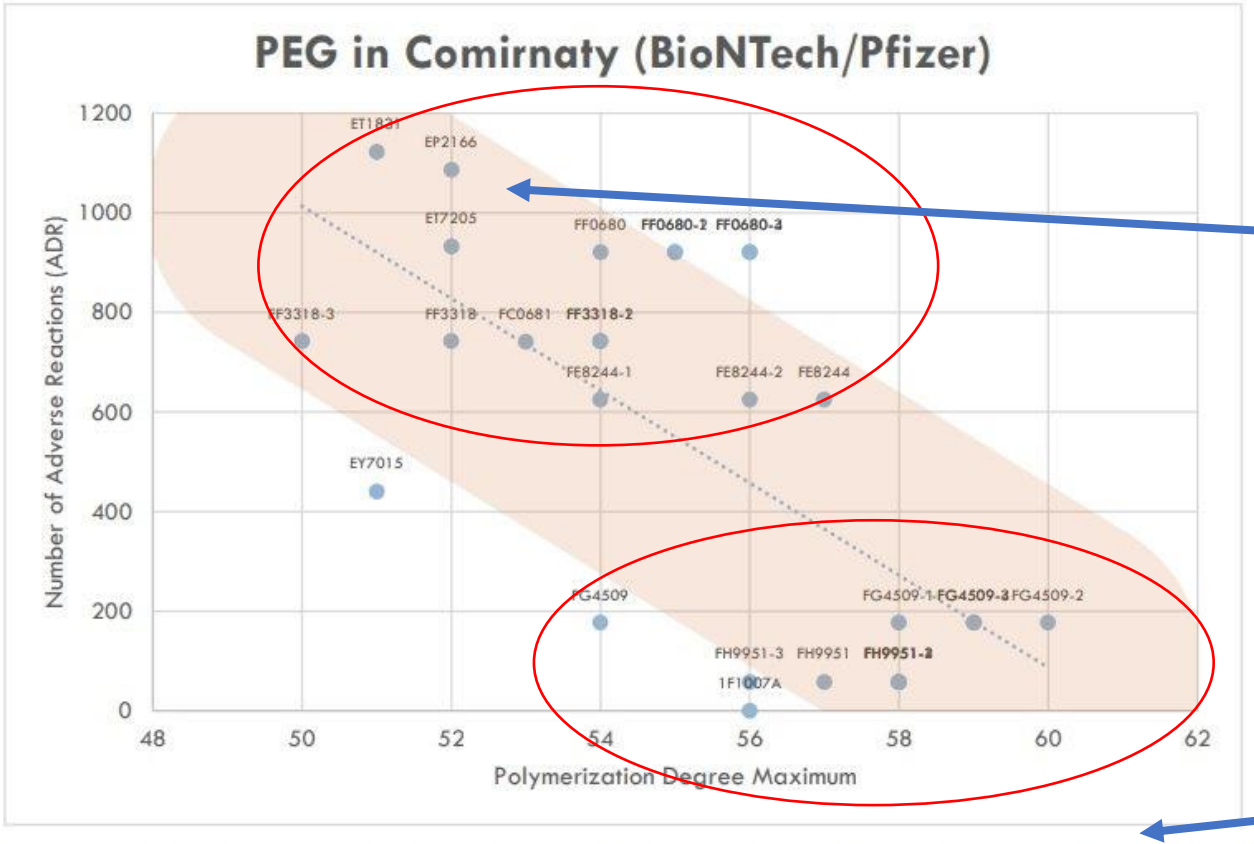
5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

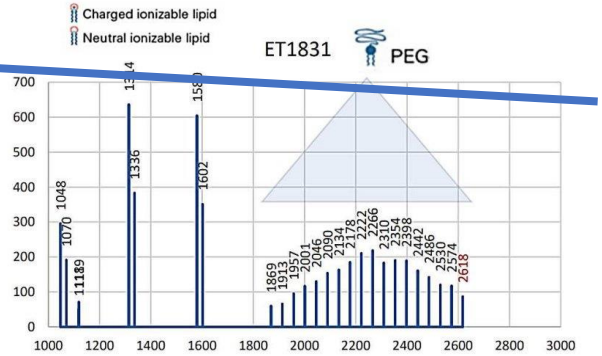
General toxicity
Rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity
Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity
Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.



Je länger der PEG- Schwanz, desto geringer die Nebenwirkung



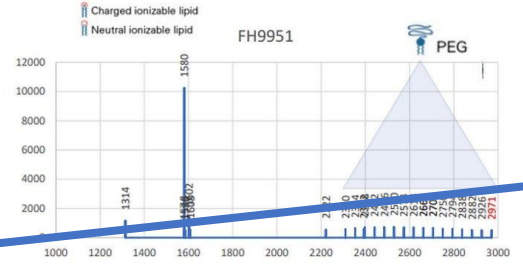


Figure 7: *From the mass spectra of samples from different batches of Comirnaty vaccine (BioNTech/Pfizer), the maximum chain lengths were compared with the number of reported vaccination complications. A clear correlation can be seen. The blue dots are associated with the BioNTech/Pfizer batch numbers analysed.*

(https://expertcouncil.one/wp-content/uploads/2023/03/AG-Impfstoffe-erste-Ergebnisse-Juli-2022_expertcouncil_one.pdf)

ADVANCED THERAPEUTICS
www.advtherap.com

Immunogenicity of Polyethylene Glycol Based Nanomedicines: Mechanisms, Clinical Implications and Systematic Approach

Nicola d'Avanzo, Christian Celia, Antonella Barone, Maria Carafa, Luisa Di Marzio, Hélder A. Santos, and Massimo Fresta**

peated administrations.[48,49] In particular, it was demonstrated that the second administration of PEGylated nanocarriers was rapidly cleared from the blood circulation, when administered at a specific time course after the injection of the first dose.[50,51] This unexpected pharmacokinetic modification, or accelerated blood clearance (ABC)[52,53] phenomenon, caused a large accumulation of PEGylated nanocarriers in the liver and it was widely studied by Dams et al. and Ishida and Kiwada using PEGylated liposomes.[54,55] This phenomenon is true for PEGylated nanocar-

tibody titer has significantly increased, and recently Yang et al. reported an incidence of anti-PEG antibodies of 72% on normal healthy patients that never interacted with PEGylated drugs. The meta-analysis of this data demonstrated that the distribution of anti-PEG antibodies in the selected cohort of healthy patients was: 18% responsiveness to IgG, 25% responsiveness to IgM, and 30% responsiveness to both anti-PEG antibodies.[22] In this study, Yang and co-workers highlighted that there was an increase in healthy patients that are positive of anti-PEG antibodies in

Je länger der PEG Schwanz – desto mehr Platz für anti-PEG Antikörper?

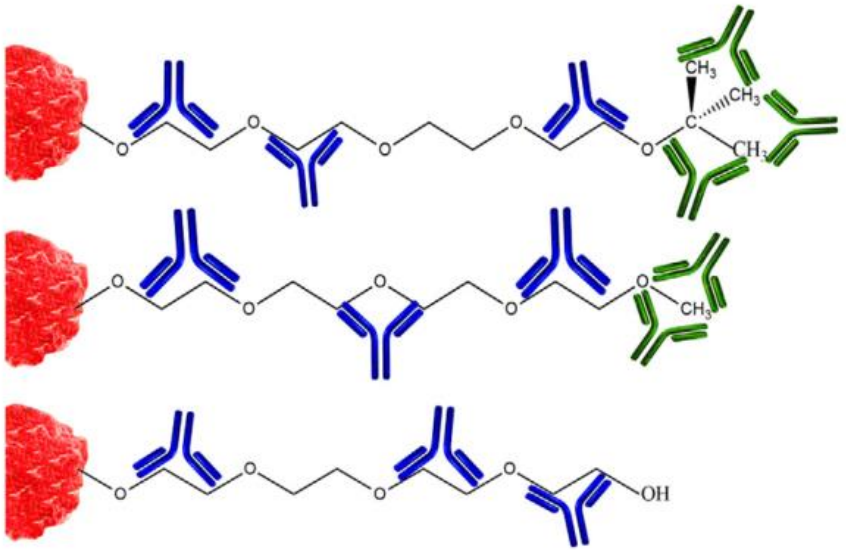
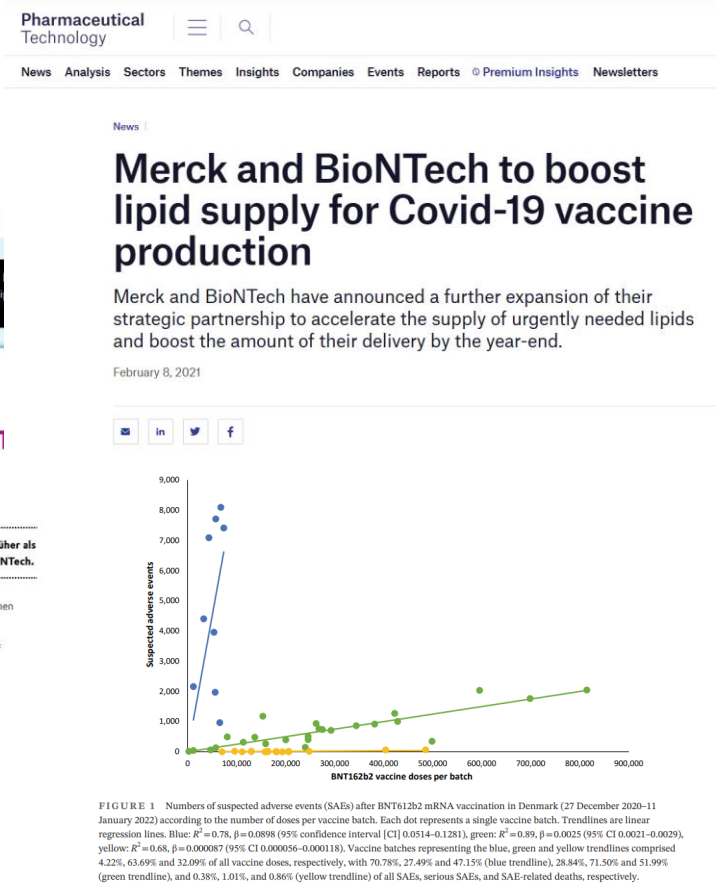


Figure 1. Schematic representation of different anti-PEG antibodies. The blue immunoglobulin is directed versus the backbone of the polymer, while the green antibodies are specific for the end-group. The picture shows that the immunogenicity of PEG is directly related to the hydrophobicity of the end-chain.

https://onlinelibrary.wiley.com/doi/abs/10.1002/adtp.201900170

=== Zulieferer für Nanolipide ===

1. **Croda** = Avanti (haben Avanti aus “Project Lightspeed” 2020 gekauft)
2. **Merck** ab Februar 2021 zusätzlich ab 2022 mit seiner im Februar 2022 für 750-780 Millionen USD gekauften Firma Exelead
3. **Evonik** ab April 2021



https://drbine.substack.com/p/liste-der-biontech-zulieferer-work

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101

https://www.docdroid.net/xq0Z8B0/pfizer-report-japanese-government-pdf#page=16

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)							% of Administered Dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

DNA contaminant

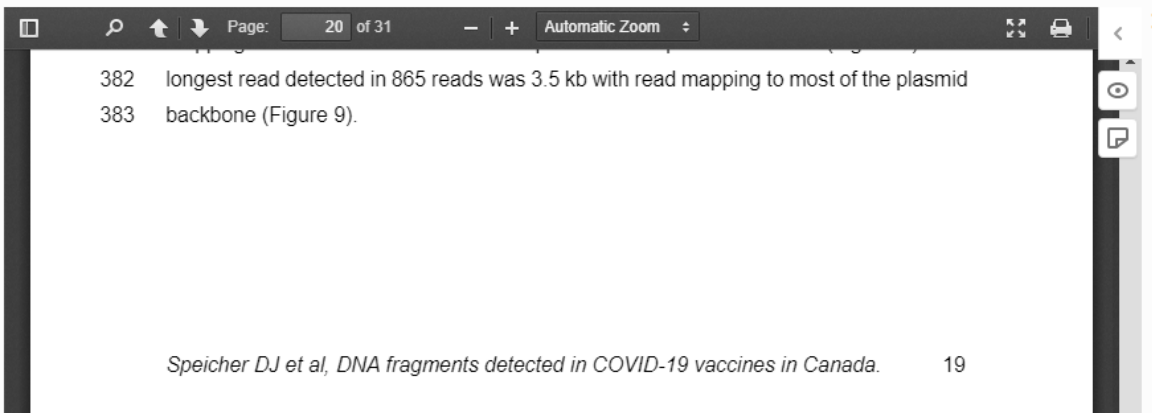
Kevin McKernan

DNA fragments detected in monovalent and bivalent Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events.

AUTHORS
David J Speicher, Jessica Rose, L. Maria Gutschi, David M Wiseman PhD, Kevin McKernan

AUTHOR ASSERTIONS

Conflict of Interest: Yes ▾ Public Data: Available ▾ Preregistration: Not applicable ▾



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Abstract

Background: In vitro transcription (IVT) reactions used to generate nucleoside modified RNA (modRNA) for SARS-CoV-2 vaccines currently rely on an RNA polymerase transcribing from a DNA template. Production of modRNA used in the original Pfizer randomized clinical trial (RCT) utilized a PCR-generated DNA template (Process 1). To generate billions ...

See more

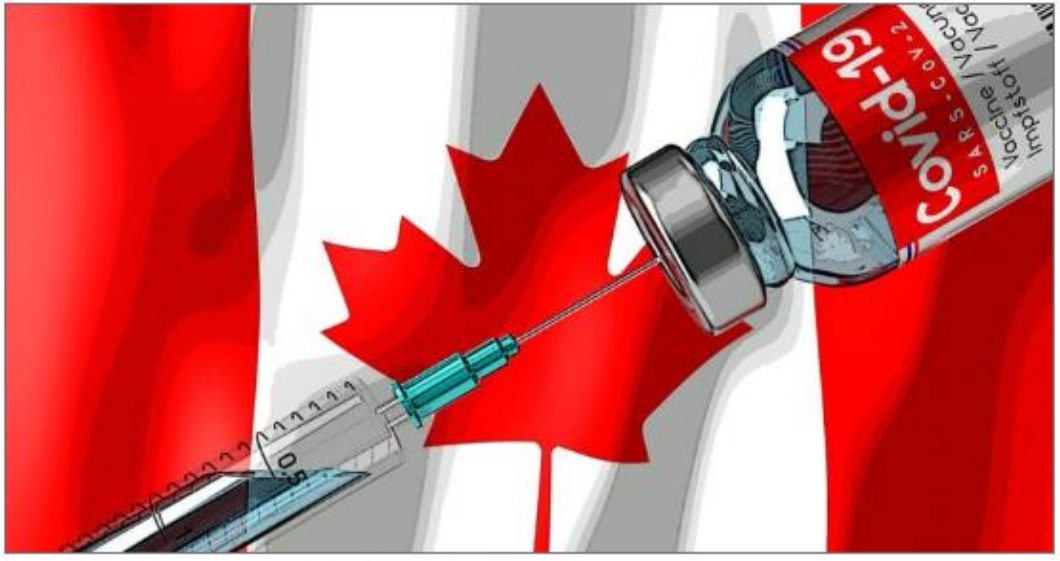
https://osf.io/mjc97/

10/20/23 • COVID › NEWS

‘An Admission of Epic Proportions’: Health Canada Confirms DNA Plasmid Contamination of COVID Vaccines

Health Canada on Thursday confirmed the presence of DNA contamination in Pfizer COVID-19 vaccines and also confirmed that Pfizer did not disclose the contamination to the public health authority.

By Michael Nevradakis, Ph.D.



In what one scientist described as an “admission of epic proportions,” Health Canada on Thursday confirmed the presence of DNA contamination in Pfizer COVID-19 vaccines, and also confirmed that Pfizer did not disclose the contamination to the public health authority.

Josh Guetzkow
@joshg99

What?!?
In 2022 & 2023, the FDA cited significant violations at an EU facility where Pfizer's mRNA 'drug substance' is purified prior to LNP encapsulation. Violations including failure to assure compliance w/specifications & standards for endotoxin testing.
But there's more! 🧵

Post vertalen

> Observation 3
>
> Laboratory procedures or testing to assure compliance with established specifications and standards is not available. Specifically,
>
> a. Standard operation procedure Doc No.: RL-TP-00048, Prufung auf Bakterien-Endotoxin: Kinetic-Turbidmetrischer Test/Testing on Bacterial Endotoxins: Kinetic Turbidimetric Test, Rev 14 describes the overall facility approach for drug substance in-process control and release testing, with no time limit for endotoxin testing

2:14 p.m. · 16 nov. 2023 · **14,3K** Weergaven

https://twitter.com/joshg99/status/1725140328661860754

REASON FOR SUBMISSION:
For Release

Lot Number: FL7649
Trade Name of Product: COMIRNATY
Licensed Name of Product: COMIRNATY
Marketing Authorisation Holder Name and Address: BioNTech Manufacturing GmbH, An der Goldgrube 12, 55131 Mainz, Germany
Manufacturing Site: Pfizer Manufacturing Belgium NV, PGS Puurs, Rijksweg 12, 2870 Puurs, Belgium
Marketing Authorisation Number: EU/1/20/1528

Date of Manufacture: 15-Sep-2021 **Date of Expiry:** 28-Feb-2022
Date of Fill: 27-Sep-2021

Product Information:

Drug Substance Target Concentration: [redacted]

LOT GENEALOGY

Component Description	Batch Number	Date of Manuf.	Manufacture Site	Quantity
Working Cell Bank	DW8970	07-May-2020	St. Louis Laboratories Pfizer Inc.	N/A
DNA Plasmid linearised	CPF-L022	13-Apr-2021	St. Louis Laboratories Pfizer Inc.	39.223 kg
BNT162b2 Drug Substance	21Y513C6101	21-May-2021	Pfizer ACMF	162.115 L
LNP Fabrication and Bulk Drug Product Formulation	FL1681	15-Sep-2021	Pfizer Puurs	328.10 kg
Drug Product Fill/Packaging	FL7649	15-Sep-2021	Pfizer Puurs	701572

Table 2. Drug Substance Quality Control Tests

Test	Test Method	Specification	Date of Test	Result
Clarity	Appearance (Clarity)	[redacted]	28-May-2021	1 NTU
Coloration	Appearance (Coloration)		28-May-2021	<=B9
pH	Potentiometry		28-May-2021	6.9
Content (RNA Concentration)	UV Spectroscopy		25-May-2021	2.27 mg/mL
Identity of Encoded RNA Sequence	RT-PCR		25-May-2021	Confirmed
RNA Integrity	Capillary Gel Electrophoresis		25-May-2021	69 %
5'- Cap	RP-HPLC		26-May-2021	90 %
Poly(A) Tail	ddPCR		11-Jun-2021	85 %
Residual DNA Template	qPCR		26-May-2021	220 ng DNA/mg RNA
Residual dsRNA	Immunoblot		21-Jun-2021	NMT 40 pg dsRNA/µg RNA
Bacterial Endotoxin	Endotoxin (LAL)		24-May-2021	NMT 1.0 EU/mL
Bioburden	Bioburden		21-May-2021	0 CFU/10mL

Abbreviations: NTU = Nephelometric Turbidity Units; B = brown; RT-PCR = reverse transcription polymerase chain reaction; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amebocyte lysate; EU = endotoxin unit; CFU = colony forming unit

Western blots

Figure S.2.6-15. BNT162b2 Expressed Protein Size by Western Blot

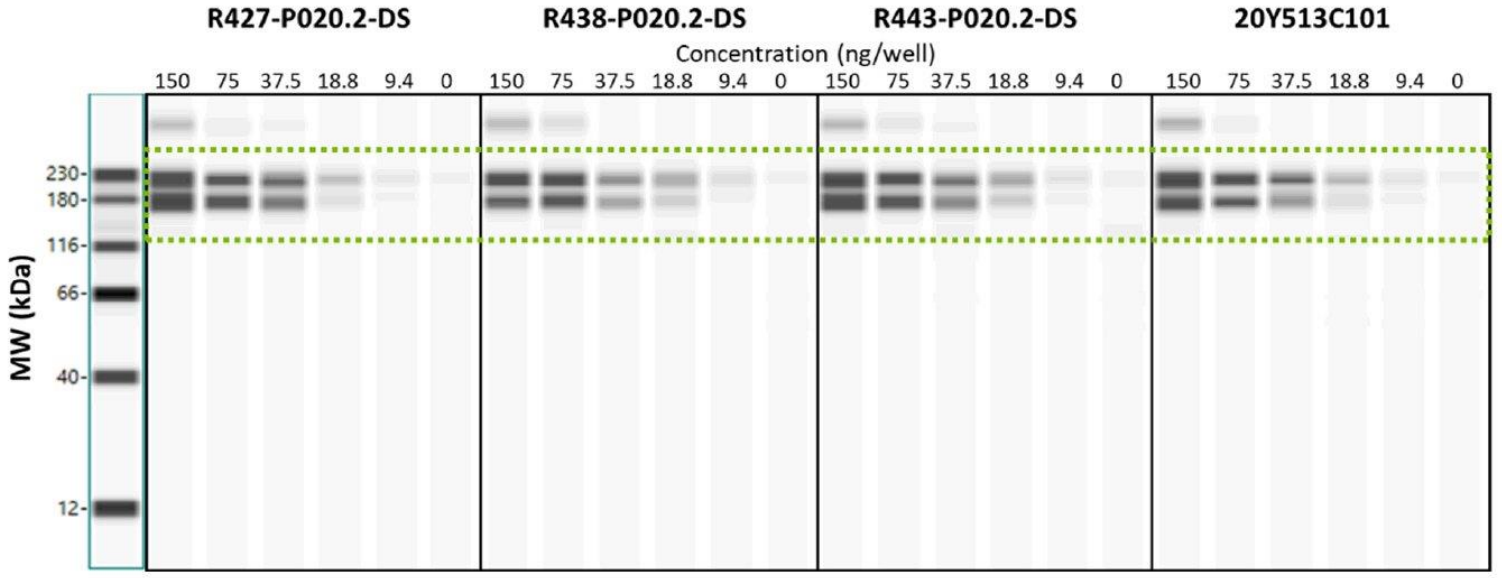


Figure S.2.6-15. To evaluate expressed protein size, BNT162b2 DS was mixed with Lipofectamine and then transfected into HEK-293 cells. Following incubation, cell lysates were evaluated for the expressed protein antigen by Western blot using an antibody specific for the SARS-CoV-2 spike protein. The first lane shows a molecular weight (MW) marker. The concentrations shown for each DS batch correspond to the amounts of DS transfected per well of HEK-293 cells.

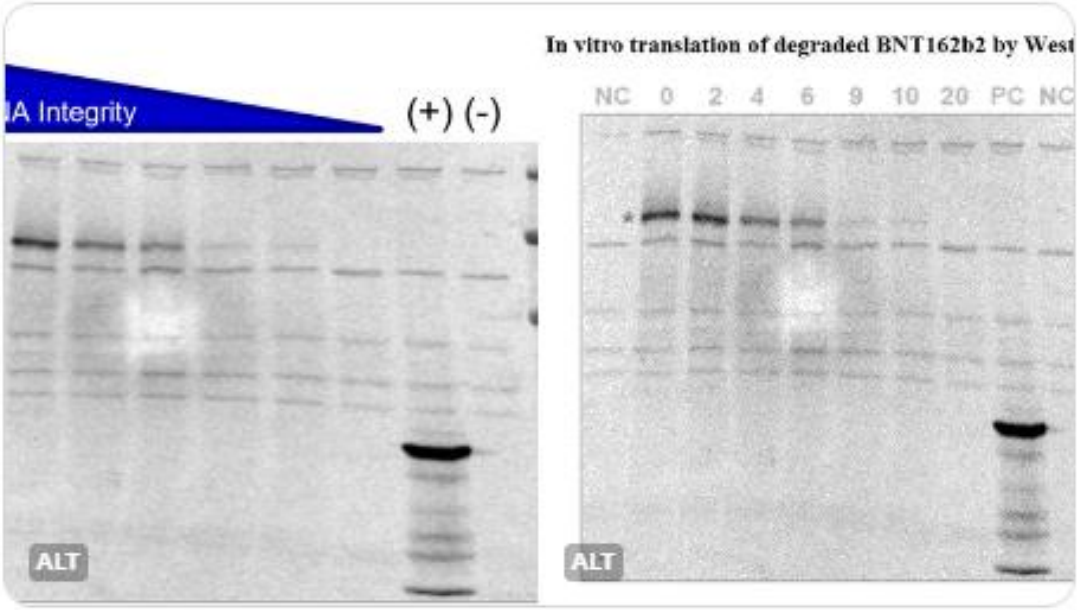
https://twitter.com/Jikkyleaks/status/1615299303643443200

Jikkyleaks
@Jikkyleaks

There was in fact one genuine-looking Western blot in the whole paper, that was meant to show that no other proteins were being produced.

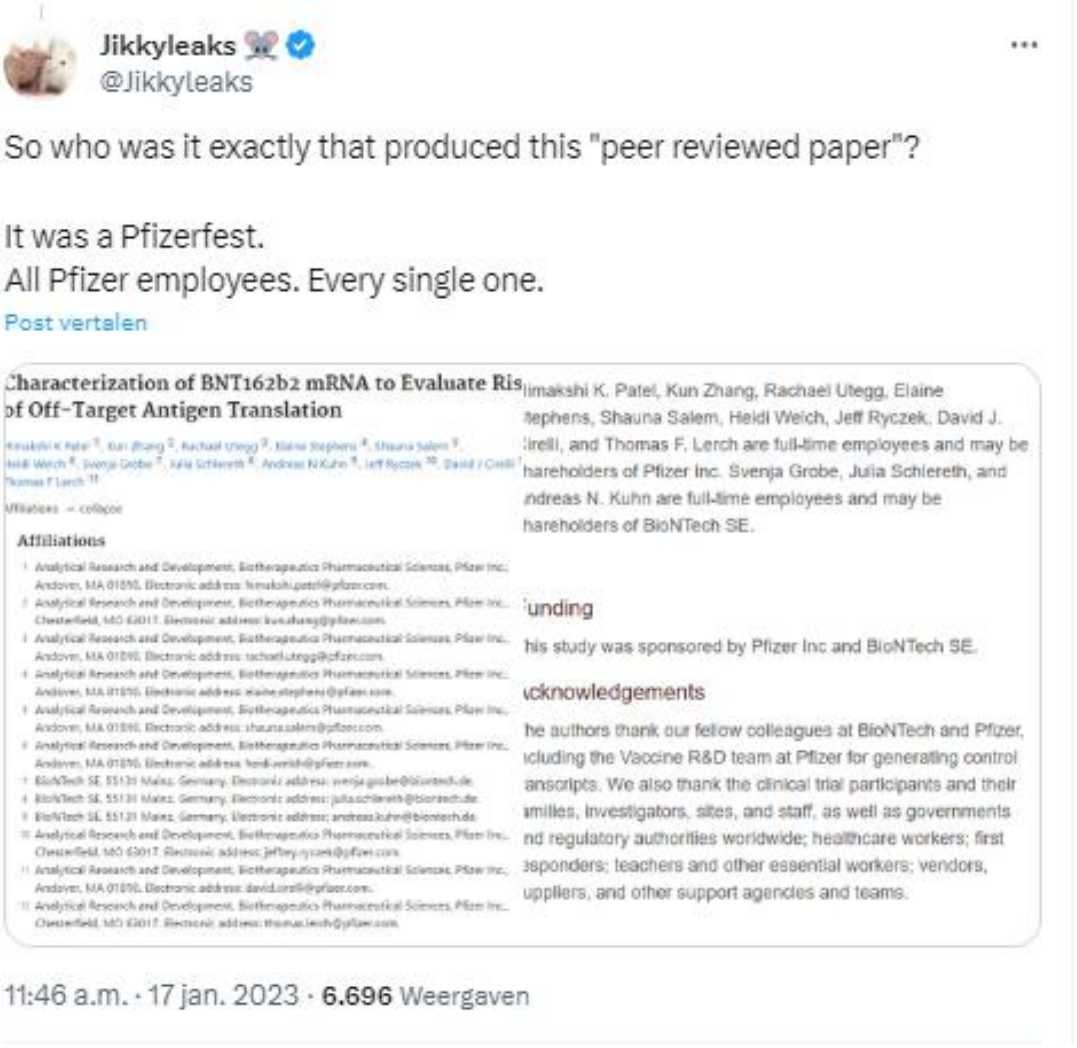
This one:

Post vertalen



11:45 a.m. · 17 jan. 2023 · **4.868** Weergaven

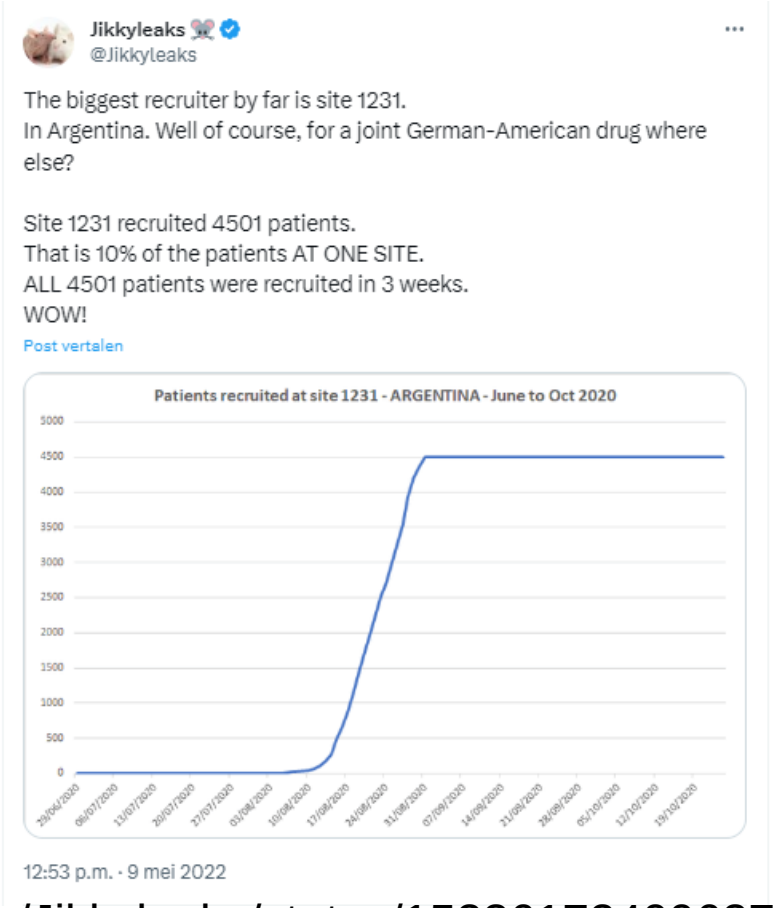
https://jpharmsci.org/action/showPdf?pii=S0022-3549%2823%2900009-6



https://twitter.com/Jikkyleaks/status/1615299423323709440

Fraud in clinical trials

Fernando Polack

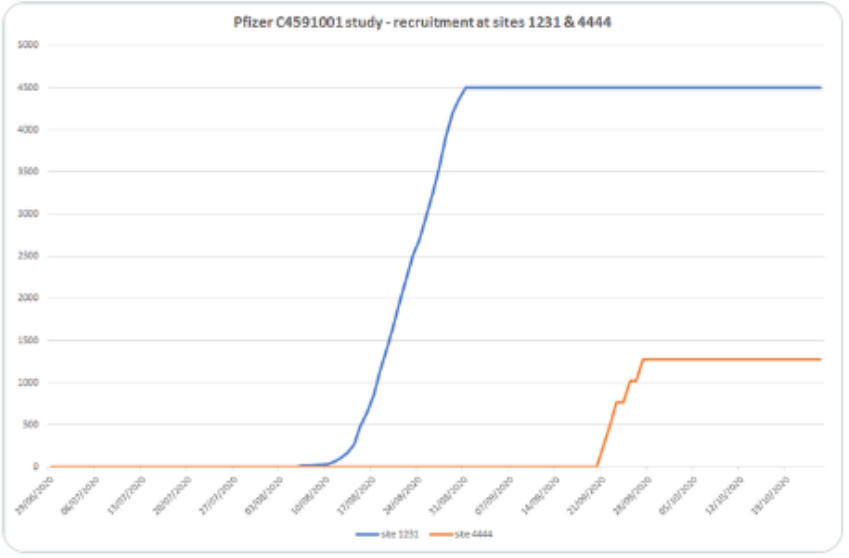


https://twitter.com/Jikkyleaks/status/1523617240062791680

Jikkyleaks 🐭
@Jikkyleaks

Well that's a bit of a problem because...
There are a lot of entries in the randomisation log for #site4444.
1275 patients to be exact.
About 3% of the total.
And you know what?
All 1275 "patients" were recruited in one week - from 22nd to 27th September 2020.

Post vertalen



12:54 p.m. · 9 mei 2022

https://twitter.com/Jikkyleaks/status/1523617314629103617

“Alarmerend en hartverscheurend” letsel door shedding bij ongevaccineerde patiënten weerspiegelt die van de COVID-vaccinininjecties zelf, aldus Dr. Pierre Kory

"Alarmerend en hartverscheurend" letsel door shedding bij ongevaccineerde patiënten weerspiegelt die van de COVID-vaccinininjecties zelf, aldus Dr. Pierre Kory

november 11, 2023 6587 23

NIEUWSBRIEF

Als ik ooit van dit blogplatform wordt verwijderd, v
gezien deze tijdsperiode NIET
ONWAARSCHIJNLIJK is, dan zal ik mijn mailingli
meenemen en ergens anders opnieuw opbouwen
maar ik zal u niet kunnen bereiken, noch zult u
weten waar u mij kunt vinden, ALS IK UW E-
MAILADRES NIET HEB. Vul het hieronder in:

Email

Abonneer

Zoeken

Zoeke

genes

MDPI

Review

The Role of miRNA Expression Profile in Sudden Cardiac Death Cases

Alessia Bernini Di Michele [1], Valerio Onofri [2], Mauro Pesaresi [1] and Chiara Turchi [1,*]

check for updates

Citation: Bernini Di Michele, A.; Onofri, V.; Pesaresi, M.; Turchi, C. The Role of miRNA Expression Profile in Sudden Cardiac Death Cases. *Genes* **2023**, *14*, 1954. https://doi.org/10.3390/genes14101954

Academic Editor: Fulvio Cruciani

Received: 6 September 2023
Revised: 11 October 2023
Accepted: 16 October 2023
Published: 17 October 2023

3. Conclusions

In this review, we have summarized experiments, evidence, and results of different studies on the implication of miRNAs in SCD cases. We compared result data from different biological starting materials showing their respective advantages and disadvantages. Moreover, we considered data on miRNA expression on tissue (fresh-frozen tissue and FFPE tissue), circulating cell-free miRNAs in whole blood, and exosomal miRNAs analyzed from serum of people who died from SCD.

The common objective of these studies is to further investigate the role of miRNAs as potential biomarkers to discriminate the causes of cardiac death. Although some studies analyzed the same miRNA types, they did not reach the same results. Some miRNAs are taken into consideration in multiple studies, such as miRNA-499a-5p, miRNA-133a, miRNA-208b, miRNA-221, and miRNA-1, and they are studied both in tissue and in blood circulation. These miRNAs have a different expression level compared to control cases, as reported in Supplementary Table S1, where we can compare the level of expression of each

The immunological interplay between vaccination and the intestinal microbiota

Petra Zimmermann

npj Vaccines **8**, Article number: 24 (2023) | Cite this article

Vaccination is the most cost-effective life-saving medical intervention[1]. However, substantial variation in individual immune responses to vaccination exists[2]. Lower vaccine immunogenicity, especially to oral vaccines, is often reported in developing countries[3,4,5]. Many intrinsic and extrinsic factors, such as age, genetics, pre-existing immunity, nutritional status and comorbidities contribute to the variations in vaccine responses[6].

https://www.nature.com/articles/s41541-023-00627-

Suspension by national institute

§ 3. Schorsing, wijziging en intrekking van de handelsvergunning

Artikel 51

1 Het College schorst een handelsvergunning, wijzigt deze of trekt deze in indien:

a. het geneesmiddel schadelijk is,

b. de therapeutische werking ontbreekt dan wel indien de afweging van voordelen en risico's niet gunstig is,

c. het geneesmiddel niet de opgegeven kwalitatieve en kwantitatieve eigenschappen bezit,

d. de krachtens artikel 42 overgelegde gegevens en bescheiden onjuist zijn of niet zijn gewijzigd overeenkomstig artikel 49,

e. de in artikel 28, eerste lid, bedoelde controles niet hebben plaatsgevonden,

f. de etikettering of de bijsluiter niet voldoet aan de daaromtrent in hoofdstuk 7 gestelde eisen,

g. niet aan voorschriften gesteld krachtens artikel 45a of 45b is voldaan,

h. de houder van de handelsvergunning de in hoofdstuk 8 neergelegde verplichtingen niet nakomt,

i. indien de coördinatiegroep zulks op grond van artikel 107octies van richtlijn 2001/83 heeft besloten, of

j. indien de bereiding of kwaliteitscontrole door de fabrikant niet in overeenstemming is met de eisen zoals beschreven in het dossier op grond waarvan de desbetreffende handelsvergunning is verleend.

5 Het College maakt een besluit tot schorsing of intrekking van een handelsvergunning toegankelijk voor het publiek.

6 Bij de toepassing van dit artikel neemt het College artikel 31, derde lid, van richtlijn 2001/83 in acht.

https://wetten.overheid.nl/BWBR0021505/2022-01-

2001/83

Article 31

1. ►M10 ↓ The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary. ◄

3. Without prejudice to paragraph 1, a Member State may, where urgent action is necessary to protect public health at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States, no later than the following working day, of the reasons for its action.

4. Where the scope of the procedure initiated under this Article, as determined in accordance with paragraph 2, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, where urgent action is necessary to protect public health, at any stage of the procedure, suspend the marketing authorisations and prohibit the use of the medicinal products concerned until a definitive decision is adopted. The Commission shall inform the Agency and the Member States no later than the following working day of the reasons for its action.

2001/83

Urgent Union procedure

Article 107i

▼M12

1. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the procedure provided for in this section by informing the other Member States, the Agency and the Commission where:

(a) it considers suspending or revoking a marketing authorisation;

(b) it considers prohibiting the supply of a medicinal product;

(c) it considers refusing the renewal of a marketing authorisation; or

(d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, the holder has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

1a. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the indications of a medicinal product is necessary. The information shall outline the action considered and the reasons therefor.

Legal route CMA

COMMISSION REGULATION (EC) No 507/2006

of 29 March 2006

on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council

Article 1

Subject matter

This Regulation lays down rules on the granting of a marketing authorisation subject to specific obligations in accordance with Article 14(7) of Regulation (EC) No 726/2004, hereinafter 'conditional marketing authorisation'.

Article 2

Scope

This Regulation shall apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation (EC) No 726/2004 and belong to one of the following categories:

1. medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;

2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;

Article 4

Requirements

1. A conditional marketing authorisation may be granted where the Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

(a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;

(b) it is likely that the applicant will be in a position to provide the comprehensive clinical data;

(c) unmet medical needs will be fulfilled;

(d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

In emergency situations as referred to in Article 2(2), a conditional marketing authorisation may be granted, subject to the requirements set out in points (a) to (d) of this paragraph, also where comprehensive pre-clinical or pharmaceutical data have not been supplied.

2. For the purposes of paragraph 1(c), 'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

2020/1043

Article 2

1. All operations related to the conduct of clinical trials, including packaging and labelling, storage, transport, destruction, disposal, distribution, supply, administration or use of investigational medicinal products for human use containing or consisting of GMOs intended to treat or prevent COVID-19, with the exception of the manufacturing of the investigational medicinal products, shall not require a prior environmental risk assessment or consent in accordance with Articles 6 to 11 of Directive 2001/18/EC or Articles 4 to 13 of Directive 2009/41/EC when these operations relate to the conduct of a clinical trial authorised in accordance with Directive 2001/20/EC.

2. Sponsors shall implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the investigational medicinal product into the environment.

3. By way of derogation from point (a) of Article 6(2) of Regulation (EC) No 726/2004 and from the second indent of the fourth paragraph of point 1.6 of Part I of Annex I to Directive 2001/83/EC, in applications for marketing authorisation for medicinal products containing or consisting of GMOs intended to treat or prevent COVID-19, **the applicant shall not be required to include a copy of the competent authority's written consent to the deliberate release into the environment of GMOs for research and development purposes in accordance with Part B of Directive 2001/18/EC**.

TFEU 168

4. By way of derogation from Article 2(5) and Article 6(a) and in accordance with Article 4(2)(k) the European Parliament and the Council, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting in order to meet common safety concerns:

(a) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;

(b) measures in the veterinary and phytosanitary fields which have as their direct objective the protection of public health;

(c) measures setting high standards of quality and safety for medicinal products and devices for medical use.

7. **Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care**. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them. The measures referred to in paragraph 4(a) shall not affect national provisions on the donation or medical use of organs

ARTIKEL II

De Regeling van de Minister van Infrastructuur en Waterstaat van 27 oktober 2020, nr. IENW/BSK-2020/143803 houdende het tijdelijk deels buiten toepassing verklaren van het Besluit genetisch gemodificeerde organismen milieubeheer 2013 en het intrekken van de Tijdelijke regeling afwijkende behandeling vergunningaanvragen gentherapie in verband met bestrijding COVID-19 ter uitvoering van verordening (EU) 2020/1043 van het Europees Parlement en de Raad betreffende de uitvoering van klinische proeven met geneesmiddelen voor menselijk gebruik die geheel of gedeeltelijk uit genetisch gemodificeerde organismen bestaan en die bestemd zijn voor de behandeling of de voorkoming van de coronavirusziekte, alsmede de levering van die geneesmiddelen (PbEU 2020, L 231) (Stcrt. 2020, 54619) wordt ingetrokken.

ARTIKEL III

Deze regeling treedt in werking met ingang van 1 januari 2023.

Deze regeling zal met de toelichting in de Staatscourant worden geplaatst.

De Staatssecretaris van Infrastructuur en Waterstaat,
V.L.W.A. Heijnen

https://www.loketgentherapie.nl/sites/default/files/2023-01/stcrt-2022-33100%20Wijziing%20Rggo%201%20januari%202023.pdf

27 428

Beleidsnota Biotechnologie

28 663

Milieubeleid

Nr. 326

BRIEF VAN DE STAATSSECRETARIS VAN INFRASTRUCTUUR EN MILIEU

Aan de Voorzitter van de Tweede Kamer der Staten-Generaal

Den Haag, 8 februari 2016

Wetenschappers hebben recentelijk, onder andere in het tijdschrift *Science* [1], opgeroepen om naast de kansen en mogelijkheden, ook aandacht te hebben voor veiligheidsmaatregelen als het gaat om genetische modificatie met een «gene drive».

https://zoek.officielebekendmakingen.nl/kst-27428-

Verbeterplan gentherapie

Opgesteld door Bureau GGO

Versie 31 oktober 2019

https://open.overheid.nl/documenten/ronl-514c5815-85a8-4582-99cc-9f8766a11319/pdf

2.1 Maatregel 1: Beschikbare capaciteit bij Bureau GGO

Resultaat:
Capaciteit is toereikend voor tijdige afhandeling vergunningaanvragen.

Omschrijving:
Inmiddels heeft het RIVM de capaciteit bij Bureau GGO voor de afhandeling van gentherapiedossiers vergroot van 2,5 fte naar 4 fte. Op basis van een inschatting van te verwachten vergunningaanvragen en aan de hand van monitoring van ontwikkelingen wordt deze capaciteit continu aangepast naar behoefte en waar dit eventueel aan de orde is wordt de noodzaak tot additionele financiële middelen met IenW opgenomen en afgehandeld.
Momenteel vindt werving plaats van een nieuwe medewerker.

Wanneer:
Per heden.

Randvoorwaarden:
- Beschikbaarheid capaciteit Bureau GGO op managementniveau RIVM en IenW gemonitord en indien nodig bijgestuurd.
- Beschikbaarheid adequaat gekwalificeerde kandidaten in arbeidsmarkt.
- Zo nodig herprioritering taken en inzet beschikbare capaciteit.

Vraag 4
Kunt u de doelen rond het verminderen van verschillen tussen Nederland en andere EU-lidstaten SMART formuleren?

Antwoord 4
Zoals beschreven in het antwoord op vraag 2 worden, met inachtneming van het behoud van de veiligheid voor mens en milieu, de knelpunten met betrekking tot proceduretermijnen voor vergunningverlening, aansluiting bij Europees afgesproken informatievereisten voor vergunningverlening en Europese openbaarheidsvereisten, opgelost met het maatregelenpakket dat in de Kamerbrief van 14 oktober 2019 is omschreven.

Het verder verminderen van verschillen tussen Nederland en andere EU-lidstaten wordt nagestreefd door bij de Europese Commissie en de lidstaten, overeenkomstig de beleidslijn die is beschreven in de genoemde Kamerbrief, in te zetten en aan te dringen op herziening van de Europese ggo-regelgeving. Daartoe zijn inmiddels eerste stappen gezet. In het Raadsbesluit van 8 november jl. heeft de Raad de Commissie verzocht een studie uit te voeren naar regelgevingsopties. Naar het oordeel van Nederland dienen deze, naast landbouwtoepassingen, ook betrekking te hebben op medische toepassingen in de biotechnologie, waaronder gentherapie[1]. Nederland heeft de nieuwe Europese Commissaris schriftelijk van deze inzet op de hoogte gesteld.

https://open.overheid.nl/documenten/ronl-8c36172f-19bf-45a5-bc02-db82b4cbc416/pdf

Vraag 42
Kunt u toelichten wat met 'in beginsel' zoals geformuleerd in voorwaarde B bedoeld wordt?

Antwoord 42
Het begrip 'in beginsel' betekent in de geformuleerde voorwaarde dat er niet vanuit wordt gegaan dat het ggo zich verspreidt, maar dat een incidentele verspreiding niet kan worden uitgesloten. Dit begrip is noodzakelijk omdat de regelgeving voor ingeperkt gebruik uitsluitend geldt voor toepassingen waarvoor vaststaat dat, door de voorgeschreven inperkingsmaatregelen, verspreiding van het ggo niet kan optreden.

Bij gentherapie kan een verspreiding van het ggo optreden door directe overdracht van mens op mens of door bijvoorbeeld bloed-, weefsel- of orgaandonatie, dan wel borstvoeding of zwangerschap of in geval de proefpersoon of patiënt een ongeluk krijgt. Omdat incidentele verspreiding dus niet kan worden uitgesloten bij gentherapie is het begrip 'in beginsel' gebruikt, omdat anders elke theoretische verspreiding ertoe zou leiden dat er geen ruimte bestaat om gentherapie onder de IG regelgeving te behandelen.

Vraag 47
Wat is de definitie van gentherapie bij dit onderdeel en bij vorige onderdelen in deze Kamerbrief en hoe verhoudt zich die tot de definitie van medische ggo-producten?

Antwoord 47

Hoewel er diverse omschrijvingen van gentherapie circuleren is er geen wettelijke definitie van dit begrip. Loket Gentherapie van het RIVM verstaat het volgende onder gentherapie: 'Klinisch onderzoek in mensen waarbij handelingen uitgevoerd worden met een genetisch gemodificeerd organisme (ggo's), of waarbij genetisch gemodificeerde cellen in het menselijk lichaam kunnen ontstaan of waarbij wijzigingen worden aangebracht in het erfelijk materiaal van menselijke cellen'. Medische producten die ggo's bevatten of daaruit bestaan (medische ggo-producten) is een meer juridische beschrijving van wat in het spraakgebruik onder gentherapie wordt verstaan. Daarnaast wordt in richtlijn 2001/83/EG de term "Advanced Therapy Medicinal Products (ATMP)" gebruikt, waaronder gentherapie eveneens valt.

Datum	13 maart 2020
Betreft	Beleidsstandpunt COGEM-advies Beoordeling van risico's voor derden bij klinisch onderzoek met gentherapie

Geachte voorzitter,

Op 23 januari 2020 zond ik u als bijlage bij mijn antwoorden op schriftelijke vragen[1], het advies van de Commissie Genetische Modificatie (COGEM) inzake de beoordeling van risico's voor derden bij klinisch onderzoek met gentherapie (CGM/200123-01). In het antwoord op vraag 31 heb ik u toegezegd om mijn beleidsstandpunt over dit advies zo spoedig mogelijk aan u te doen toekomen. Hierbij doe ik u het toegezegde beleidsstandpunt toekomen, mede namens de minister voor Medische Zorg en Sport (MZS).

https://open.overheid.nl/documenten/ronl-94022902-92b4-44b0-b218-

Motie

Motie van het lid Veldman c.s. over de procedures voor klinische onderzoeken met spoed versnellen

Download

26 maart 2020

25295-180

Motie

Ondertekenaars

Eerste ondertekenaar
H.S. Veldman, Tweede Kamerlid

Mede ondertekenaar
R.A.A. Jetten, Tweede Kamerlid

THE NETHERLANDS, PAYS-BAS, NEDERLAND

House of Representatives, Chambre des représentants, Tweede Kamer der Staten-Generaal

Mr / M.	Habbo Siebold (Hayke)	Veldman	Head of Delegation, Chair of the Standing Committee on European Affairs	Alliance of Liberals and Democrats for Europe, ALDE

https://www.tweedekamer.nl/kamerstukken/moties/detail?id=2020D11846&did=2020D11846

35 676

Initiatiefnota van het lid Veldman over anticiperen op toekomstscenario's: beschikbaarheid van vaccins en antibiotica met behulp van reële optiewaarden

Nr. 1

GELEIDENDE BRIEF

Aan de Voorzitter van de Tweede Kamer der Staten-Generaal

Den Haag, 14 december 2020

Hierbij bied ik u aan de «Initiatiefnota van het lid Veldman over anticiperen op toekomstscenario's: beschikbaarheid van vaccins en antibiotica met behulp van reële optiewaarden».

Veldman

Ontwikkeling van vaccins

Vaccins bevatten van oudsher vaak verzwakte ziekteverwekkers die worden ingespoten, zodat er een immuunrespons op gang komt. Innovaties, zoals DNA-technieken, hebben bestaande vaccins verbeterd en de ontwikkeling van nieuwe vaccins mogelijk gemaakt[9]. De (door)ontwikkeling van vaccins is een kostenintensief proces, waarbij een aantal vragen van belang zijn, te weten: is er vraag naar een vaccin tegen een bepaalde ziekte? Hoe maakt de bacterie of het virus iemand ziek? Hoe reageert het immuunsysteem hierop en is het aannemelijk dat dat met een vaccin te beïnvloeden is? Is het veilig om het vaccin te ontwikkelen en toe te dienen? Gedurende fasen van klinisch onderzoek worden vaccins in onderzoeksetting – net als geneesmiddelen – uitvoerig getest op kwaliteit, werkzaamheid en veiligheid[10]. Het College ter Beoordeling van Geneesmiddelen (CBG) of de *European Medicines Agency* (EMA), besluit op basis van de klinische data over markttoelating.

https://zoek.officielebekendmakingen.nl/dossier/kst-35676-

COM(2020)261 - *Regulation*
Conduct of clinical trials with and supply of medicinal products for human use containing or consisting of GMOs intended to treat or prevent coronavirus disease

2. Key dates

Document	17-06-2020
Online publication	17-06-2020
Decision	15-07-2020; Verordening 2020/1043
Publication in Official Journal [i]	17-07-2020; OJ L 231 p. 12-16

https://www.eumonitor.eu/9353000/1/j9vvik7m1c3gyxp/vl9le5ff3dyr

EUROPEAN COMMISSION

Brussels, 17.6.2020

COM(2020) 245 final

COMMUNICATION FROM THE COMMISSION

EU Strategy for COVID-19 vaccines

---

1. AN URGENT NEED FOR ACTION

The COVID-19 pandemic is inflicting huge human and economic costs on the European Union and the world. A permanent solution to this crisis is most likely to be brought about by the development and deployment of an effective and safe vaccine against the virus.

https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1597339415327&uri=CELEX:52020DC0245

2.1. An EU approach for efficiency and solidarity

The EU Member States are closely interlinked. The Single Market, allowing the free movement of goods and people, has allowed economies to integrate closely and has increased the interdependence of all our economies and societies. As the pandemic moves across borders, so its socio-economic impact on each of the Member States spreads to the others. Against that background, it is essential that all 27 EU Member States have access to a vaccine as early as possible. The same applies to the Member States of the European Economic Area (EEA).

Joint action at EU level is the surest, quickest and most efficient way of achieving that objective. No Member State on its own has the capacity to secure the investment in developing and producing a sufficient number of vaccines. A common strategy allows better hedging of bets, sharing of risks and pooling investments to achieve economies of scale, scope and speed.

An important step towards joint action between Member States has already been taken in the formation of an inclusive vaccine Alliance by France, Germany, Italy, and the Netherlands. This alliance was formed to pool the national resources of those countries and secure fair access to vaccine supplies for the European population. The current proposal builds on the important groundwork undertaken by that Alliance.

In order to scale this approach up to cover the whole EU, the Commission proposes to run a central procurement process, which creates a number of important advantages. In particular, all EU Member States will be able to benefit from an option to purchase vaccines via a single procurement action. This process also offers vaccine producers a significantly simplified negotiation process with a single point of contact, thus reducing costs for all. Centralising vaccine procurement at EU level has the merit of speed and efficiency by comparison with 27 separate processes. A truly European approach would avoid competition between Member States. It creates solidarity between all Member States, irrespective of the size of their population and their purchasing power. A pan-EU approach will increase the EU's leverage when negotiating with industry. It will also enable us to combine the scientific and regulatory expertise of the Commission and the Member States.

A common EU approach will always respect the principle of subsidiarity and Member States' competences in health policy: vaccination policies remain in the hands of Member States.

Contract for possible coronavirus vaccine for Europe

News item | 13-06-2020 | 15:00

The vaccine alliance formed by France, Germany, Italy and the Netherlands reached agreement with AstraZeneca today on supplying a coronavirus vaccine. If development of the vaccine is successful, the pharmaceutical company will be able to provide Europe with 300 to 400 million doses of vaccine in stages from the end of 2020, health minister Hugo de Jonge wrote in a letter to parliament today.

Earlier this month France, Germany, Italy and the Netherlands joined forces to form the Inclusive Vaccine Alliance, in order to have a stronger negotiating position in the race for a coronavirus vaccine.

https://www.government.nl/latest/news/2020/06/13/contract-for-possible-coronavirus-vaccine-for-europe

2009/120

2. DEFINITIONS

For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

2001/83

article 1

4. Immunological medicinal product: Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) "allergen product" shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

2003/63

part III

1.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on "Active substance(s)", the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this Annex:

- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

- A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on "Quality Data" as delineated in Part I of this Annex:

2019/5

Article 2

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is amended as follows:

(1) in Article 1, the following point is inserted:

'26a. Variation or variation to the terms of a marketing authorisation:

An amendment to the contents of the particulars and documents referred to in:

(a) Article 8(3) and Articles 9 to 11 of this Directive and Annex I thereto, Article 6(2) of Regulation (EC) No 726/2004 and in Article 7 of Regulation (EC) No 1394/2007; and

(b) the terms of the decision granting the marketing authorisation for a medicinal product for human use, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet related to changes to the summary of the product characteristics.';

(2) Article 23b is amended as follows:

(a) paragraphs 1 to 4 are replaced by the following:

'1. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon.

2. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the competent authority.

2a. The Commission is empowered to adopt delegated acts in accordance with Article 121a in order to supplement this Directive by:

(a) specifying the categories in which variations shall be classified; and

(b) establishing procedures for the examination of applications for variations to the terms of marketing authorisations.

3. When adopting the delegated acts referred to in this Article, the Commission shall endeavour to make possible the submission of a single application for one or more identical changes made to the terms of different marketing authorisations.

'Article 121a

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 22b, 23b(2a), 47, 52b and 54a shall be conferred on the Commission for a period of five years from 28 January 2019. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3. The delegation of power referred to in Articles 22b, 23b(2a), 47, 52b and 54a may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making ([*8]).

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Articles 22b, 23b(2a), 47, 52b and 54a shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and to the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

([*8]) OJ L 123, 12.5.2016, p. 1.'."

TFEU 290

Article 290

1. A legislative act may delegate to the Commission the power to adopt non-legislative acts of general application to supplement or amend certain non-essential elements of the legislative act.

The objectives, content, scope and duration of the delegation of power shall be explicitly defined in the legislative acts. The essential elements of an area shall be reserved for the legislative act and accordingly shall not be the subject of a delegation of power.

2. Legislative acts shall explicitly lay down the conditions to which the delegation is subject; these conditions may be as follows:

(a) the European Parliament or the Council may decide to revoke the delegation;

(b) the delegated act may enter into force only if no objection has been expressed by the European Parliament or the Council within a period set by the legislative act.

For the purposes of (a) and (b), the European Parliament shall act by a majority of its component members, and the Council by a qualified majority.

3. The adjective 'delegated' shall be inserted in the title of delegated acts.

II

(Non-legislative acts)

REGULATIONS

COMMISSION DELEGATED REGULATION (EU) 2021/756

of 24 March 2021

amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

(Text with EEA relevance)

2021/756

(2) In point (a) of Article 23(1*a*) the following point (ix) is added:

'(ix) variations related to changes to the active substance of a human coronavirus vaccine, including replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences;'

(3) In point 1 of Annex I, point (c) is replaced by the following:

'(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, with the exception of:

— changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

— replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;

— replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

— replacement of a strain for a veterinary vaccine against equine influenza;'

(4) In point 2 of Annex II the following point (l) is added:

'(l) variations related to the replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine.'

EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

Expert group Human Pharmaceutical Committee
19 February 2021

Expert group Human Pharmaceutical Committee
DRAFT AGENDA

Friday, 19 February 2021 (10:00 – 12:00)

1. Introductory comments.

2. Discussion on the draft delegated act amending Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use

3. AOB

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE DELEGATED ACT

Article 23b of Directive 2001/83/EC[1] and Article 16a of Regulation (EC) No 726/2004[2] empower the Commission to adopt delegated acts specifying the categories in which variations to authorised human medicinal products are to be classified; and establishing procedures for the examination of applications for variations to the terms of marketing authorisations.

This Delegated Regulation amends Commission Regulation (EC) No 1234/2008[3] by adding provisions to deal with variations to the active substance of authorised COVID-19 vaccines.

2. CONSULTATIONS PRIOR TO THE ADOPTION OF THE ACT

Member States' experts were consulted in the context of the Pharmaceutical Committee[4], which discussed the matter on 19 February 2021.

https://ec.europa.eu/transparency/expert-groups-register/screen/meetings/consult?lang=en&meetingId=24156&fromExpertGroups=2858

3. LEGAL ELEMENTS OF THE DELEGATED ACT

The legal basis of this Delegated Regulation is Article 23b of Directive 2001/83/EC and Article 16a of Regulation (EC) No 726/2004, which empower the Commission to adopt delegated acts specifying the categories in which variations are to be classified; and establishing procedures for the examination of applications for variations to the terms of the marketing authorisation.

The delegated powers should be used to amend Commission Regulation (EC) No 1234/2008, which governs the examination of variations for medicinal products for human use and veterinary medicinal products.

The proposed changes to Commission Regulation (EC) No 1234/2008 address the need to specify the applicable provisions for adaptations of the active substance of authorised COVID-19 vaccines in order to ensure their effectiveness against mutations or variants of the virus that may evolve over time. In this regard, it seems appropriate to use procedures that have been established for human influenza vaccines in the context of a pandemic. This will ensure the streamlined handling of any variation and enable the competent authorities to respond to specific needs arising from the COVID-19 pandemic and the associated public health crisis. It seems appropriate to extend the coverage of the new provisions to all coronaviruses, again building on the approach used in the past for human influenza vaccines, where the provisions are applicable to all forms of human influenza.

Article 23(1a) is amended as follows:

(a) The following point (ix) is added to point (a):

'(ix) variations related to changes to the active substance of a human coronavirus vaccine, including replacement or addition of a serotype, strain or antigen or combination of serotypes, strains or antigens;'

In Annex I, point 1 (c) is replaced by the following:

- '(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, with the exception of:

– changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

– replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a human coronavirus vaccine;

– replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

– replacement of a strain for a veterinary vaccine against equine influenza;'

In Annex II The following point (l) is added to point 2:

- '(l) variations related to the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a human coronavirus vaccine.'

Key players

Key players PDF

European Parliament

Committee responsible	Rapporteur	Appointed
ENVI Environment, Public Health and Food Safety	renew europe. Chair on behalf of committee CANFIN Pascal	09/03/2021

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FIND OUT WHAT WE DO TO:

- Strengthen democracy and transparency
- Create jobs and opportunities
- Lead the digital transformation
- Make Europe stronger in the world
- Combat climate change

Pascal Canfin is a Renew member of the European Parliament and chair of the Environment Committee. He is also the deputy secretary general of Renaissance, President Emmanuel Macron's party, and believes that the governing coalition is "in a moment of healing" after "the shock" from using Article 49.3 of the Constitution to pass the pension reform bill without a vote in Parliament. He says "the fundamental combat is to prevent Marine Le Pen from coming to power."

Pascal CANFIN

Renew Europe Group

Member

France - Liste Renaissance (France)

Date of birth : 22-08-1974 , Arras

https://oeil.secure.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2021/2616(DEA)&l=en

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Summary

-

Policy Area

Health and Food Safety - SANTE

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Phase

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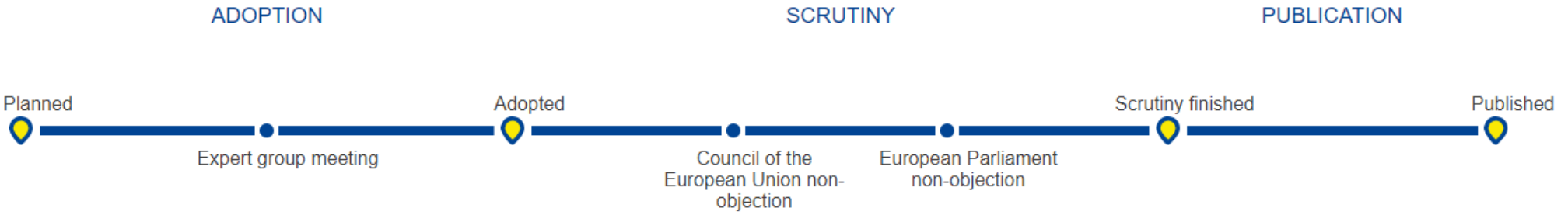
Scrutiny period

1 month for the Council of the European Union
3 months for the European Parliament



Delegated act details

Title

Commission Delegated Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Text with EEA relevance)

Short title

B5 - CIS 1501430 - ISC amending Regulation (EC) 1234/2008-CG

Basic legislative act

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance)

- *Article - 16 bis, Paragraph - 3.*

https://webgate.ec.europa.eu/regdel/#/delegatedActs/1677

Documents

Type	Institution	Date	Actions
Delegated act	European Commission	10 May 2021	
Parliament Plenary	European Parliament	05 May 2021	
Parliament Motion Commitee	European Parliament	23 April 2021	
Delegated act adopted	European Commission	24 March 2021	
Agenda	European Commission	19 February 2021	
Draft delegated act	European Commission	19 February 2021	

2021/756

(2) In point (a) of Article 23(1*a*) the following point (ix) is added:

'(ix) variations related to changes to the active substance of a human coronavirus vaccine, including replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences;'

(3) In point 1 of Annex I, point (c) is replaced by the following:

'(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, with the exception of:

— changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

— replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;

— replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

— replacement of a strain for a veterinary vaccine against equine influenza;'

(4) In point 2 of Annex II the following point (l) is added:

'(l) variations related to the replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine.'

Supervised Fraud

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This is the English translation of Betrug unter Aufsicht.

Betrug unter Aufsicht

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This article is a summary of my findings thus far, and provides citeable sources for my Corona-Ausschuss-Interview claims.

The PHMPT FOIA production of the 16+ BNT162b2 FDA BLA license is scheduled to be completed in December 2023 [1]; in other words, the two outstanding productions contain the ~150,000 most explosive pages - a good time to review what we have. That being said, there is only so much space in an article. I have left out a **lot** of findings.

https://modarnlife.substack.com/p/supervised-fraud