Prof. Jörg Matysik
Analytische Chemie, Univ. Leipzig

Die Analytik der mRNA-Impfstoffe am Paul-Ehrlich-Institut: Eine persönliche Bestandsaufnahme

Sächsischer Landtag, UA Corona
Do., 23. April 2026

Ich wurde im Okt. & Nov. 2021 mit Comirnaty **2x geimpft**.

Kanzlei Rogert & Ulbrich, Düsseldorf:
Meine beiden Chargen (**1F1010A** und **SDEH4**) stehen auf den nicht ungefährlichen Plätzen 30 und 96

1 Farbe

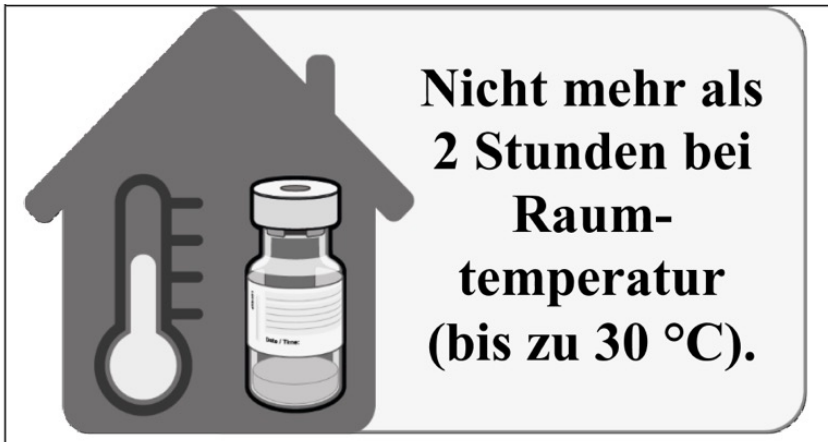
2 Toxizität

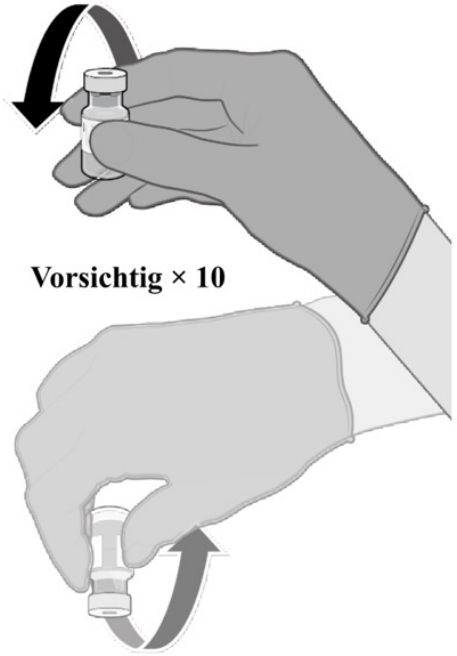
3 Qualitätskontrolle

1 Beipackzettel für Ärzte

Thermisch und
mechanisch **empfindlich**!

Soll **„grauweiß“** sein.
Ist das „hellgrau“?
Bei **Verfärbung** nicht verwenden!





- Drehen Sie die verdünnte Dispersion 10-mal vorsichtig um. Nicht schütteln.
- Der verdünnte Impfstoff sollte als grauweiße Dispersion ohne sichtbare Partikel vorliegen. Verwenden Sie nicht den verdünnten Impfstoff, wenn Partikel oder Verfärbungen vorhanden sind.

4

1

Assessment report on extension of marketing authorisation
EMA/719541/2021

Table 1. Composition of BNT162b2 Tris/Sucrose Finished Product, 30 µg RNA Volume, 6 Dose Multi-dose Vial

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)
BNT162b2 drug substance	In-house specification	Active ingredient	0.1
ALC-0315	In-house specification	Functional lipid	1.43
ALC-0159	In-house specification	Functional lipid	0.18
DSPC	In-house specification	Structural lipid	0.31
Cholesterol	Ph. Eur.	Structural lipid	0.62
Sucrose	USP-NF, Ph. Eur.	Cryoprotectant	103
Tromethamine (Tris base)[b]	USP-NF, Ph. Eur.	Buffer component	0.20
Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl)[c]	In-house specification	Buffer component	1.32
Water for Injection	USP-NF, Ph. Eur.	Solvent/vehicle	q.s.

Quelle: EMA

Keine Substanz mit Eigenfarbe erkennbar.
Keine hellgraue Farbe durch Absorption dieser Zutaten.

1 Physikalische Ursachen von Farben

(1) **ABSORPTION VON LICHT**

(2) **STREUUNG VON LICHT**:

- **Rayleigh-Streuung,** wenn Partikel kleiner als Wellenlänge des Lichts (380-780 nm):
  Blau wird stärker gestreut als rot.
  Blaue Farbe des Himmels.

- **Mie-Streuung**, wenn Partikel groß wie Wellenlänge des Lichts:
  Alle Farben werden gleichmäßig gestreut.
  Agglomeration führt zur Mie-Streuung.

Impfstoff soll **„grauweiß“** sein.
Bei **Verfärbung** nicht verwenden!

1

LNP Size	Dynamic Light Scattering (DLS)	40 to 180 nm

„LNP size for drug product is measured by dynamic light scattering (DLS) and the efficacy of the drug product depends on the size of the LNP.

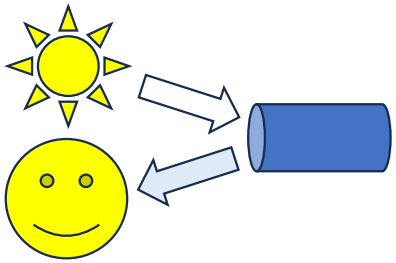
The proposed acceptance criteria of 40 to 180 nm seem wide compared to clinical batch data that is found in the range of 59-74 nm for the small scale clinical batches (“classical“ LNP process) and 68-71 nm for the emergency supply (“upscale” LNP process).

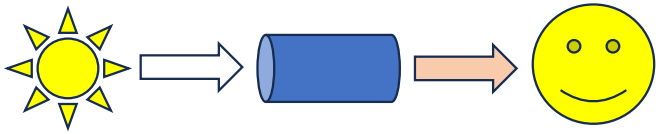
The acceptance criteria should therefore be tightened to be in line with what has been qualified in the clinical studies or clinically qualified by other means and set such that a clinically qualified level is assured throughout the shelf-life of the drug product."

Quelle: „Rapporteur’s Rolling Review assessment report" des "Committee for Medicinal Products for Human Use (CHMP)“ (19.11.2020)

„Kleine klinische Ansätze“ und „große Notfalls-Ansätze“ haben also unterschiedliche Eigenschaften. Welcher wird denn nun untersucht?
Jedenfalls sind beides **Rayleigh-Streuer.**

1





Remission
(Aufsicht)

(im Tageslicht)

Transmission
(Durchsicht)

Diese Nanopartikel sind **Rayleigh-Streuer.**

Haben also Ärzte die (nicht-agglomerierte = intakte) farbige Substanz verworfen, während sie eine (agglomerierte = verdorbene) graue Substanz verimpften?

1 Vorschrift aus der *Eur. Ph.*: „Appearance“.

EUROPEAN PHARMACOPOEIA 10.5

01/2021:20202
corrected 10.5

2.2.2. DEGREE OF COLORATION OF LIQUIDS(1)

◊A solution is *colourless* if it has the appearance of *water R* or the solvent used for the preparation of the solution to be examined, or is not more intensely coloured than reference solution B_9.

Report the results together with the method used (method I, method II or method III).

European Pharmacopoeia revises gene coloration of liquids

At its 165th session in November 2019, the European Pharmacopoeia Commission adopted a new version of one of its widely used general methods, **chapter *2.2.2. Degree of coloration of liquids***, which has been extensively revised to include the instrumental method. The revised chapter will be published in European Pharmacopoeia (Ph. Eur.) Supplement 10.3, available in July 2020 (implementation date: 1 January 2021).

This chapter now describes three methods:

- in **method I** (visual method), the colours are compared in diffused daylight, viewing horizontally against a white background;
- in **method II** (visual method), the colours are compared in diffused daylight, viewing vertically against a white background;
- **method III** is the instrumental method – this part of the text has been harmonised with the USP and the JP in the Pharmacopoeial Discussion Group (PDG).

Diese Vorschrift ist für Flüssigkeiten, die streuen, nicht geeignet!

Keine Angabe, welche Methode (I, II oder III) verwandt wird.

PEI-Oberchargenprüfer Dr. W. beschrieb Experiment vor BVerwG (Sommer 2022) anders.

1

Berliner Zeitung 26. Jan. 2022

Berliner Zeitung: *Die Chemiker sind besorgt über die Angabe, dass die Dispersion „grau“ sein könne. Sie sehen darin ein mögliches Problem der Reinheit. Wie sieht BioNTech dies?*

Antwort von BioNTech:

Nein. Die Wahrnehmung einer Färbung des Impfstoffs ist im Beipackzettel beschrieben und kein Hinweis auf mögliche Verunreinigungen. Der Terminus „weiße bis grauweiße Dispersion“ ist ein „Terminus technikus“, der bei der Beschreibung pharmazeutischer Produkte verwendet wird. Im Englischen lautet er „white to off-white“. Dies entspricht im Deutschen am ehesten der Bezeichnung „gebrochenes Weiß“ oder „Cremeweiß“ – und weniger einem „grau“. Produkte, die Nanopartikel enthalten, zeichnen sich im Allgemeinen durch diese Eigenschaft aus.

„cremeweiß“:
Widerspricht Beipackzettel
(“grauweiß“)

„Trübung“:
Passt nicht zu Beipackzettel
(„Partikel sichtbar“)

Die Trübung beeinflusst die Qualität des Impfstoffes nicht, sondern ergibt sich lediglich aus der Lichtstreuung an den Lipid-Nanopartikeln. Ein vergleichbarer Effekt führt auch zur weißen Farbe bei Milch. Hier entsteht der Eindruck der weißen Milch durch die Streuung und Reflektion des Lichtes durch die Fettkügelchen in der Oberflächenschicht. Wie die Autoren selbst beschrieben haben, sind nicht alle verwendeten Inhaltsstoffe farblos, daher ist unter bestimmten Bedingungen der Eindruck einer leichten Färbung normal.

„nicht farblos“: falsch!

Leichte Verfärbung also doch „normal“?!

1 Fazit

Beipackzettel:
Intakte Substanz sei **farblos**, ist aber **Rayleigh-Streuer** (blauer Himmel).

Verdorbene Substanz ist „verfärbt“, wäre aber **Mie-Streuer** (graue Regenwolke).

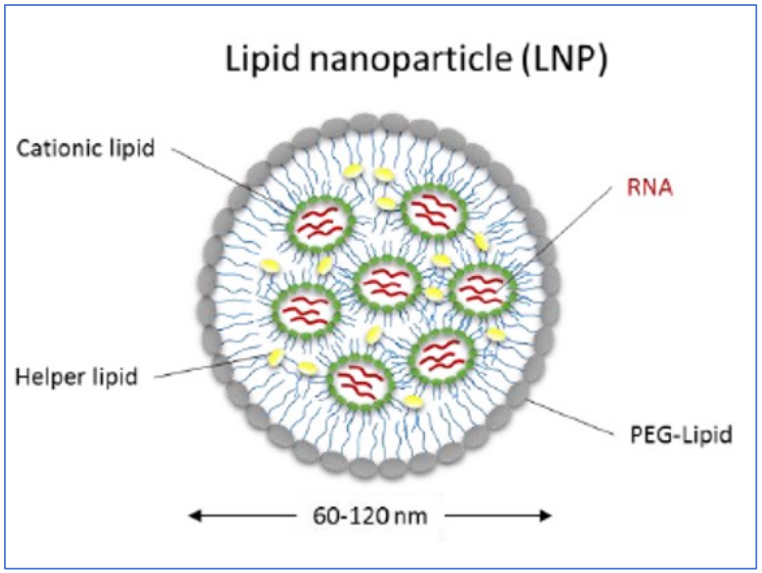
Nach dem Beipackzettel ist unverdorbenes Produkt zu verwerfen,
während verdorbenes (agglomeriertes) Produkt empfohlen wird.

Antwort von BioNTech:
Widerspricht dem eigenen Beipackzettel: „cremeweiß“, „Verfärbung normal“.

Behauptet unwahr, dass auch wir Chemiker der Ansicht sein, dass nicht alle Substanzen farblos sein.

Analytisches Protokoll nach *Eu. Ph:*
untauglich für **lichtstreuende** Substanzen.

1



Struktur-Modell von BioNTech.

ACS NANO

www.acsnano.org

Mesoscopic Structure of Lipid Nanoparticle Formulations for mRNA Drug Delivery: Comirnaty and Drug-Free Dispersions

Tobias Unruh,* Klaus Götz, Carola Vogel, Erik Fröhlich, Andreas Scheurer, Lionel Porcar, and Frank Steiniger

Cite This: *ACS Nano* 2024, 18, 9746–9764

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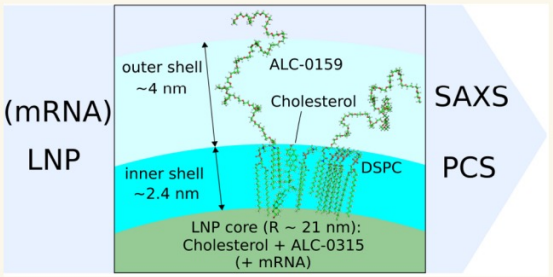
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Lipid nanoparticles (LNPs) produced by anti-solvent precipitation (ASP) are used in formulations for mRNA drug delivery. The mesoscopic structure of such complex multicomponent and polydisperse nanoparticulate systems is most relevant for their drug delivery properties, medical efficiency, shelf life, and possible side effects. However, the knowledge on the structural details of such formulations is very limited. Essentially no such information is publicly available for pharmaceutical dispersions approved by numerous medicine agencies for the use in humans and loaded with mRNA encoding a mimic of the spike protein of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) as, e.g., the Comirnaty formulation (BioNTech/Pfizer). Here, we present a simple preparation method to mimic the Comirnaty drug-free LNPs including a comparison of their structural properties with those of Comirnaty. Strong evidence for the liquid state of the LNPs in both systems is found in contrast to the designation of the LNPs as solid lipid nanoparticles by BioNTech. An exceptionally detailed and reliable structural model for the LNPs i.a. revealing their unexpected narrow size distribution will be presented based on a combined small-angle X-ray scattering and photon correlation spectroscopy (SAXS/PCS) evaluation method. The results from this experimental approach are supported by light microscopy, ^{1}H NMR spectroscopy, Raman spectroscopy, cryogenic electron microscopy (cryoTEM), and simultaneous SAXS/SANS studies. The presented results do not provide direct insights on particle formation or dispersion stability but should contribute significantly to better understanding the LNP drug delivery process, enhancing their medical benefit, and reducing side effects.



KEYWORDS: *lipid nanoparticles (LNPs), BNT162b2 Comirnaty, small-angle X-ray scattering (SAXS), dynamic light scattering (DLS, PCS), mRNA drug delivery, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), proton nuclear magnetic resonance spectroscopy (^{1}H NMR)*

ARTICLE

1 Farbe

2 Toxizität

3 Qualitätskontrolle

2 Toxizität

(a) Nanopartikel
(b) N^1-Methyl*p*seudouridin
(c) Lipid ALC-315
(d) DNA-Reste
(e) Spike-Proteine
(f) Sicherheitsdatenblatt
(g) Anreicherung in Leber

2a

Review

Lipid Nanoparticles as Active Biointerfaces: From Membrane Interaction to Systemic Dysregulation

Falko Seger [1], L. Maria Gutschi [2] and Stephanie Seneff [3,*]

[1] Independent Researcher, Berlin, Germany, 10117

[2] Pharmacy Consultant, Retired, Ottawa, Canada K1P 1C1

[3] Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge MA USA 02139

: Stephanie Seneff seneff@csail.mit.edu

Abstract

Lipid nanoparticles (LNPs) are central to modern mRNA therapeutics, including COVID-19 vaccines. Far from passive carriers, their ionizable lipids actively interact with cellular membranes. Evidence from cellular, transcriptomic, and proteomic studies indicates that LNPs, with or without nucleic acid, alter gene and protein expression, thereby initiating inflammatory, detoxification, and stress responses at the membrane. Key pathways affected include lipid metabolism and detoxification, with roles for Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and cytochrome P450 enzymes. We hypothesize that the phosphatidylinositol (PI) cycle is the primary site of LNP-induced perturbations, regulating membrane restructuring and organelle trafficking during endocytosis. Disruption of this cycle triggers downstream signaling cascades, including Nuclear Factor kappa B (NF-κB), Mitogen-Activated Protein Kinases (MAPKs), Janus kinase/signal transducers and activators of transcription (JAK/STAT), and Mechanistic Target of Rapamycin (mTOR). We term this systemic effect lipid-nanoparticle-driven membrane dysfunction (L-DMD), characterized by dysregulated cellular communication, stress responses, and energy balance. This review provides a mechanistic framework for understanding the persistent biological effects of modified modRNA-LNP exposure and emphasizes a systems-level intracellular perspective.

2a

Nature Communications

https://doi.org/10.1038/s41467-026-71295-1

Article in Press

Mitochondrial vulnerability underlies myocarditis from COVID-19 mRNA vaccine

Received: 20 August 2025

Accepted: 18 March 2026

Go Mori, Masayoshi Yamamoto, Kaori Ishikawa, Hiroaki Tamashiro, Hayate Suzuki, Seiya Mizuno, Kazuto Nakada & Atsushi Kawaguchi

LNPs components cause myocarditis in mice

Although RNA modifications such as $m^1\psi$ and m^7GpppN significantly attenuate immune activation, synthetic mRNA delivered by LNPs can still elicit inflammatory responses through innate immune sensors, including TLRs and RLRs[28–30]. It is also reported that lipid components

2b

https://de.wikipedia.org/wiki/N1-Methylpseudouridin

Nicht angemeldet Diskussionsseite Beiträge Benutzerkonto erstell

Artikel Diskussion Lesen Bearbeiten Quelltext bearbeiten Versionsgeschichte Wikipedia durchsuchen

N^1-Methylpseudouridin

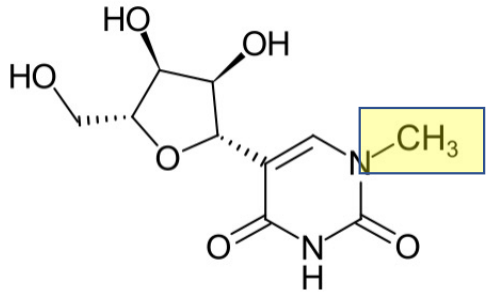
N^1-Methylpseudouridin (abgekürzt *m1Ψ*) ist ein synthetisches Nukleosid aus der Gruppe der Pyrimidine. Es wird in der Biochemie und Molekularbiologie bei der In-vitro-Transkription verwendet und kommt in den SARS-CoV-2-Impfstoffen Tozinameran (synonym *BNT162b2*) und mRNA-1273 vor.

Eigenschaften [Bearbeiten | Quelltext bearbeiten]

N^1-Methylpseudouridin ist das methylierte Derivat des Pseudouridins. Es wird in der In-vitro-Transkription unter anderem zur Herstellung von RNA-Impfstoffen verwendet,[2][3] da im Vergleich zu Uridin und Analoga bei einer Anwendung in Wirbeltieren deutlich weniger Aktivierung der angeborenen Immunantwort auftritt.[4] Gleichzeitig ist die Translation stärker.[5][6] Bei der Proteinbiosynthese wird es wie Uridin gelesen und ermöglicht vergleichsweise hohe Ausbeuten an Protein.[6][7] Im Jahr 2016 wurde eine vereinfachte Synthese publiziert.[8]

Einzelnachweise [Bearbeiten | Quelltext bearbeiten]

1. ↑ Dieser Stoff wurde in Bezug auf seine Gefährlichkeit entweder noch nicht eingestuft oder eine verlässliche und zitierfähige Quelle hierzu wurde noch nicht gefunden.

Strukturformel


Allgemeines	
Name	N^1-Methylpseudouridin
	• m1Ψ (Kurzcode)

Deshalb: „mod-RNA“ und der Firmenname „Moderna“.

Weniger Entzündung, stabiler, aber bleibt im Stoffwechsel.

2b

Article

N^1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting

https://doi.org/10.1038/s41586-023-06800-3

Received: 25 January 2023

Accepted: 31 October 2023

Published online: 6 December 2023

Open access

Check for updates

Thomas E. Mulroney[1], Tuija Pöyry[1], Juan Carlos Yam-Puc[1], Maria Rust[1], Robert F. Harvey[1], Lajos Kalmar[1], Emily Horner[1], Lucy Booth[1], Alexander P. Ferreira[1], Mark Stoneley[1], Ritwick Sawarkar[1], Alexander J. Mentzer[2], Kathryn S. Lilley[3], C. Mark Smales[4,5], Tobias von der Haar[4], Lance Turtle[6], Susanna Dunachie[7,8,9], Paul Klenerman[7,10], James E. D. Thaventhiran[1,11]✉ & Anne E. Willis[1,11]✉

In vitro-transcribed (IVT) mRNAs are modalities that can combat human disease, exemplified by their use as vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). IVT mRNAs are transfected into target cells, where they are translated into recombinant protein, and the biological activity or immunogenicity of the encoded protein exerts an intended therapeutic effect[1,2]. Modified ribonucleotides are commonly incorporated into therapeutic IVT mRNAs to decrease their innate immunogenicity[3–5], but their effects on mRNA translation fidelity have not been fully explored. Here we demonstrate that incorporation of N^1-methylpseudouridine into mRNA results in +1 ribosomal frameshifting in vitro and that cellular immunity in mice and humans to +1 frameshifted products from BNT162b2 vaccine mRNA translation occurs after vaccination. The +1 ribosome frameshifting observed is probably a consequence of N^1-methylpseudouridine-induced ribosome stalling during IVT mRNA translation, with frameshifting occurring at ribosome slippery sequences. However, we demonstrate that synonymous targeting of such slippery sequences provides an effective strategy to reduce the production of frameshifted products. Overall, these data increase our understanding of how modified ribonucleotides affect the fidelity of mRNA translation, and although there are no adverse outcomes reported from mistranslation of mRNA-based SARS-CoV-2 vaccines in humans, these data highlight potential off-target effects for future mRNA-based therapeutics and demonstrate the requirement for sequence optimization.

2b

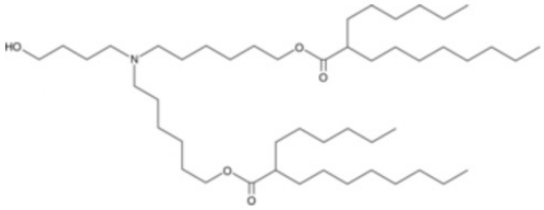
Frame shifting = Ablesefehler:

SACHSEN
TBDITFO

2c

ALC-0315

Item No. 34337



Achtung

Nur für Forschungszwecke und Laboruntersuchungen: Nicht für die Anwendung im oder am Menschen!

0.4 mg dieser Substanz subkutan.

„May cause cancer“

“Causes skin irritation“

“Causes serious eye irritation“

Seit Februar 2022 ist der Hinweis „may cause cancer“ gelöscht

Cayman CHEMICAL

Safety Data Sheet
acc. to OSHA HCS

Printing date 09/22/2021 Revision date 09/22/2021

1 Identification

· **Product identifier**

· **Trade name: ALC-0315**

· **Article number:** 34337
· **Application of the substance / the mixture**
This product is for research use - Not for human or veterinary diagnostic or therapeutic use. It is the responsibility of the purchaser to determine suitability for other applications.

· **Details of the supplier of the safety data sheet**
· **Manufacturer/Supplier:**
Cayman Chemical Co.
1180 E. Ellsworth Rd.
Ann Arbor, MI 48108
USA

· **Information department:** Product safety department
· **Emergency telephone number:**
During normal opening times: +1 (734) 971-3335
US/CANADA: 800-424-9300
Outside US/CANADA: 703-741-5970

2 Hazard(s) identification

· **Classification of the substance or mixture**

GHS02 Flame

Flam. Liq. 2 H225 Highly flammable liquid and vapor.

GHS08 Health hazard

Carc. 1A H350 May cause cancer.

GHS07

Skin Irrit. 2 H315 Causes skin irritation.
Eye Irrit. 2A H319 Causes serious eye irritation.
STOT SE 3 H335 May cause respiratory irritation.

(Contd. on page 2)

Product Description

ALC-0315 is an ionizable amino lipid that has been used in combination with other lipids in the formation of lipid nanoparticles.[1] Administration of severe acute respiratory coronavirus 2 (SARS-CoV-2) mRNA in ALC-0315-containing lipid nanoparticles induces the production of IgG that binds to the SARS-CoV-2 receptor-binding domain (RBD) in rhesus macaques, with a boost in antigen-specific IgG geometric mean titers (GMT) seven and 14 days after a second dose. Formulations containing ALC-0315 have been used in the development of lipid nanoparticles for the delivery of mRNA-based vaccines.

WARNING This product is **not** for human or veterinary use.

https://cdn.caymanchem.com/cdn/msds/34337m.pdf

2c

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

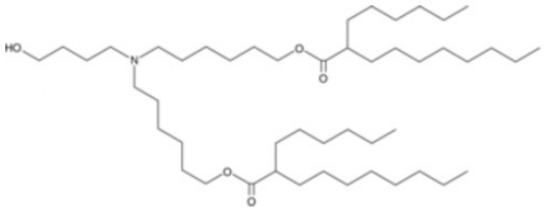
Genotoxizität ***„nicht zu erwarten“,*** weil es Lipide sind!?

Bei einem Lipid, das zum Binden ans Phosphatgerüst (d.h. an RNA) optimiert wurde?!
Es ist konstruiert, um mit RNA zu wechselwirken, diese einzupacken und in die Zelle zu transportieren.
Es gibt kein Argument, dass ALC-0315 nicht auch mit DNA wechselwirkt.

2c

ALC-0315

Item No. 34337



JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Open Access

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Communication

The Overlooked Stereoisomers of the Ionizable Lipid ALC315

Chandra Kanta De,△ Masumi Tsuda,△ Chendan Zhu,△ Stefanie Dehn, Heike Hinrichs, Nobuya Tsuji, Hui Jin, Hisashi Arase, Shinya Tanaka,* and Benjamin List*

Cite This: *J. Am. Chem. Soc.* 2025, 147, 28595–28600

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ABSTRACT: Lipid nanoparticles (LNPs) are a powerful delivery platform for nucleic acid therapeutics such as mRNA vaccines and gene therapies. Central to their success are ionizable lipids, which facilitate the cellular uptake and endosomal escape of nucleic acids. However, achieving a high delivery efficiency often comes with the drawback of increased cytotoxicity. Here, we report a chemical, biological, and toxicological investigation into the three stereoisomers of ALC315, a mixture of which constitutes one of the most successful marketed ionizable lipids for LNPs. We demonstrate that the individual stereoisomers of ALC315 can be accessed by either the asymmetric chemical synthesis or chromatography of an intermediate. An LNP formulation based on a single stereoisomer of ALC315 enhances mRNA transfer efficiency while reducing the associated cytotoxicity in human cell lines. Our results underscore the potential of stereochemically pure ionizable lipids as key components in the development of next-generation nucleic acid therapies, offering an enhanced delivery performance and better safety profiles.

Der Wirkstoff in Contergan (Thalidomid, α-Phthalimidoglutarimid) ist ebenfalls chiral.

2c

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS

Communication

The Overlooked Stereoisomers of the Ionizable Lipid ALC315

Chandra Kanta De,△ Masumi Tsuda,△ Chendan Zhu,△ Stefanie Dehn, Heike Hinrichs, Nobuya Tsuji, Hui Jin, Hisashi Arase, Shinya Tanaka,* and Benjamin List*

Journal of the American Chemical Society pubs.acs.org/JACS Communication

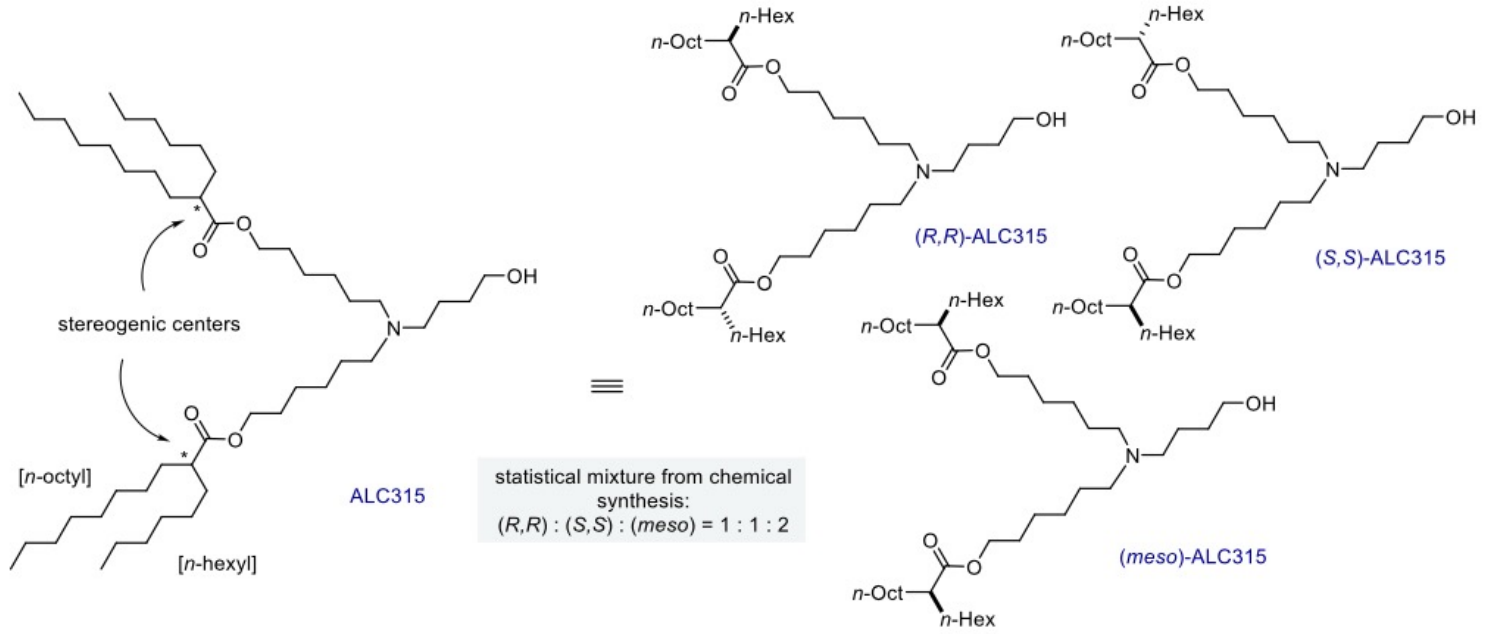


Figure 1. Stereoisomers of ALC315. ALC315 has two identical stereogenic centers and as a result exists as three different stereoisomers, (*R*,*R*)-ALC315, (*S*,*S*)-ALC315, and (*meso*)-ALC315.

2d

Science, Public Health Policy, and the Law
Volume: v5.2019-2024
December 2024
Peer Reviewed, Clinical Research

An Institute for Pure and Applied Knowledge (IPAK)

Public Health Policy Initiative (PHPI)

IPAK PHPI

BioNTech RNA-Based COVID-19 Injections Contain Large Amounts Of Residual DNA Including An SV40 Promoter/Enhancer Sequence

Ulrike Kämmerer[1], Verena Schulz[2], Klaus Steger[3*]

Abstract

Background: BNT162b2 RNA-based COVID-19 injections are specified to transfect human cells to efficiently produce spike proteins for an immune response.

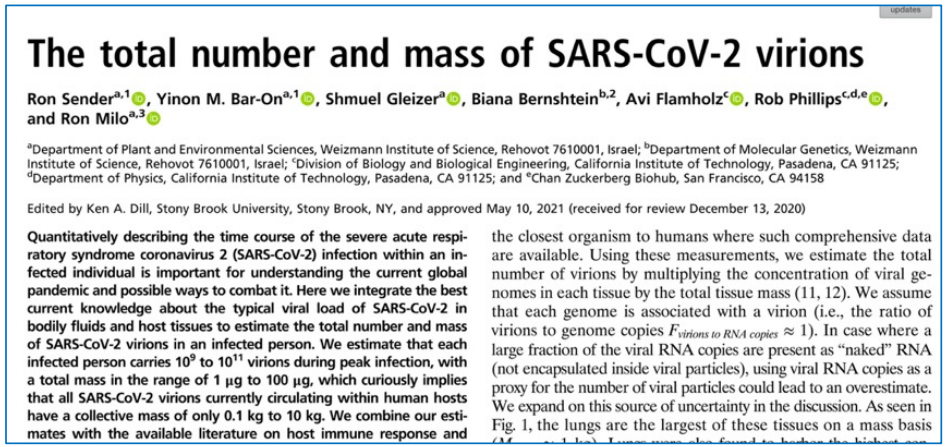
Methods: We analyzed four German BNT162b2 lots applying HEK293 cell culture, immunohistochemistry, ELISA, PCR, and mass spectrometry.

Results: We demonstrate successful transfection of nucleoside-modified mRNA (modRNA) biologicals into HEK293 cells and show robust levels of spike proteins over several days of cell culture. Secretion into cell supernatants occurred predominantly via extracellular vesicles enriched for exosome markers. We further analyzed RNA and DNA contents of these vials and identified large amounts of DNA after RNase A digestion in all lots with concentrations ranging from 32.7 ng to 43.4 ng per clinical dose. This far exceeds the maximal acceptable concentration of 10 ng per clinical dose that has been set by international regulatory authorities. Gene analyses with selected PCR primer pairs proved that residual DNA represents not only fragments of the DNA matrices coding for the spike gene, but all genes from the plasmid including the SV40 promoter/enhancer and the antibiotic resistance gene.

Conclusion: Our results raise grave concerns regarding the safety of the BNT162b2 vaccine and call for an immediate halt of all RNA biologicals unless these concerns can be dispelled.

DNA-Verunreinigungen:
30 bis 40 ng gemessen.
10 ng zulässig.

2e



The total number and mass of SARS-CoV-2 virions

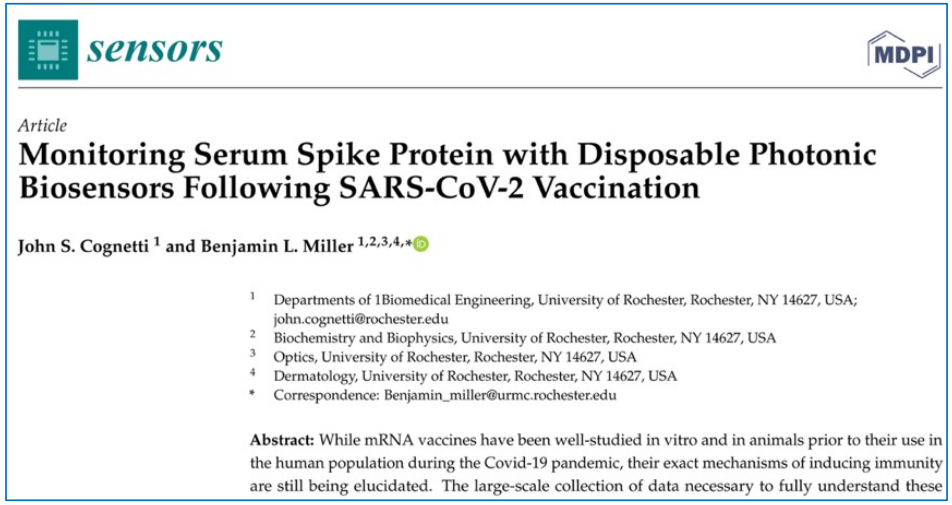
Ron Sender[a,1], Yinon M. Bar-On[a,1], Shmuel Gleizer[a], Biana Bernshtein[b,2], Avi Flamholz[c], Rob Phillips[c,d,e], and Ron Milo[a,3]

[a]Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot 7610001, Israel; [b]Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 7610001, Israel; [c]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA 91125; [d]Department of Physics, California Institute of Technology, Pasadena, CA 91125; and [e]Chan Zuckerberg Biohub, San Francisco, CA 94158

Edited by Ken A. Dill, Stony Brook University, Stony Brook, NY, and approved May 10, 2021 (received for review December 13, 2020)

Quantitatively describing the time course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within an infected individual is important for understanding the current global pandemic and possible ways to combat it. Here we integrate the best current knowledge about the typical viral load of SARS-CoV-2 in bodily fluids and host tissues to estimate the total number and mass of SARS-CoV-2 virions in an infected person. We estimate that each infected person carries 10^9 to 10^{11} virions during peak infection, with a total mass in the range of 1 μg to 100 μg, which curiously implies that all SARS-CoV-2 virions currently circulating within human hosts have a collective mass of only 0.1 kg to 10 kg. We combine our estimates with the available literature on host immune response and the closest organism to humans where such comprehensive data are available. Using these measurements, we estimate the total number of virions by multiplying the concentration of viral genomes in each tissue by the total tissue mass (11, 12). We assume that each genome is associated with a virion (i.e., the ratio of virions to genome copies $F_{virions\ to\ RNA\ copies} \approx 1$). In case where a large fraction of the viral RNA copies are present as "naked" RNA (not encapsulated inside viral particles), using viral RNA copies as a proxy for the number of viral particles could lead to an overestimate. We expand on this source of uncertainty in the discussion. As seen in Fig. 1, the lungs are the largest of these tissues on a mass basis

Infektion: Gesamtmenge **von $3 \cdot 10^{10}$ bis $3 \cdot 10^{12}$** Spike-Proteinen.



sensors

MDPI

Article

Monitoring Serum Spike Protein with Disposable Photonic Biosensors Following SARS-CoV-2 Vaccination

John S. Cognetti [1] and Benjamin L. Miller [1,2,3,4,*]

[1] Departments of 1Biomedical Engineering, University of Rochester, Rochester, NY 14627, USA; john.cognetti@rochester.edu
[2] Biochemistry and Biophysics, University of Rochester, Rochester, NY 14627, USA
[3] Optics, University of Rochester, Rochester, NY 14627, USA
[4] Dermatology, University of Rochester, Rochester, NY 14627, USA
* Correspondence: Benjamin_miller@urmc.rochester.edu

Abstract: While mRNA vaccines have been well-studied in vitro and in animals prior to their use in the human population during the Covid-19 pandemic, their exact mechanisms of inducing immunity are still being elucidated. The large-scale collection of data necessary to fully understand these

Also **≈100.000x mehr als bei Infektion**.
Zudem: andere Verteilung im Körper.
Anfrage beim PEI läuft.

Impfung: 65,7 mg Spike-Protein / Mensch.
Bei Molekularmasse von 140 kDa: **$4{,}7 \cdot 10^{17}$** Spike-Proteine.

2f

Das Comirnaty Sicherheitsdatenblatt

SICHERHEITSDATENBLATT

Überarbeitet am 13-Mai-2022 Version 2.01 Seite 1 / 12

Somit sind von den Vorgaben des Sicherheitsdatenblattes

- Ärzte
- Medizinisches Fachpersonal (MFA, MTA)
- Die Putzkolonnen der Praxen und Impfzentren
- Das Sicherheitspersonal in den Impfzentren
- Die Müllabführt, die die leeren Fläschchen entsorgt hat
- Impfende Apotheker

OEB steht für Occupational Exposure Band, was auf Deutsch die Einstufung der beruflichen Exposition, bzw. die Gefahreneinstufung ist.

2f

Eine Dosis Comirnaty (BNT162B2 oder PF-07302048) enthielt ungefähr 30 µg Produkt pro Dosis bei einer Pfizer internen Arbeitssicherheitseinstufung von OEB 5 (hohes toxisches Potential).

OEB Stufe	Toxisches Potential	Max Anwenderbelastung Gewicht/m³	Max Anwenderbelastung Gewicht/Tag
6	Extrem hohes toxisches Potential	< 200 ng	< 0,01 mg
5	Hohes toxisches Potential	< 1 µg	< 0,1 mg
4	Toxisches Potential	1-10 µg	01-1 mg
3	Mittleres toxisches Potential	10-100 µg	1-10 mg
2	Geringes toxisches Potential	100-1.000 µg	10–100 mg
1	Kein toxisches Potential	1.000-5.000 µg	> 100 mg

11

Pharmaceutical Sciences
Worldwide Research & Development
Reference Standard Certificate

STANDARD INFORMATION	
Compound	PF-07302048
Reference Standard Lot	PF-07302048-DP-RM
Reevaluation / Expiration Date	05-AUG-2021
Occupational Exposure Band	OEB 5
Long Term Storage Condition	(b) (4) °C
Short Term Storage Condition	N/A
Primary Contact	(b) (6)
Authorized By	Rebekah Ward
Authorized On	01-Feb-2021

TESTS AND RESULTS	
Fluorescence assay	
RNA Content	(b) (4) mg/mL

FOOTNOTES
Parent drug product lot (b) (4)
(b) (4) C for up to (b) (4) days if sampled aseptically

03:15 (GMT)

OEB steht für Occupational Exposure Band, was auf Deutsch die Einstufung der beruflichen Exposition, bzw. die Gefahreneinstufung ist.

2f

Wenn Sie **heute** nach diesem Datenblatt googeln, werden Sie finden, dass der Impfstoff in die (vorher offenbar unbekannte) Kategorie **„V-OEB“** gehört.
(**„V“** steht für **„vaccination“**)

OEB steht für Occupational Exposure Band, was auf Deutsch die Einstufung der beruflichen Exposition, bzw. die Gefahreneinstufung ist.

2g Anreicherungseffekte bei Nanopartikeln als Arzneiformen

22.02.22, 14:23 mRNA- und DNA-Impfstoffe: Nanotechnologie der Covid-19-Vakzinen | PZ – Pharmazeutische Zeitung

Pharmakokinetisch zeichnet sich der Impfstoff dadurch aus, dass die höchsten Konzentrationen an der Injektionsstelle gefunden werden, über die Zeit aber eine Umverteilung zu beobachten ist. Für nanopartikuläre Arzneiformen ist eine Anreicherung in der Leber typisch und auch für die LNP beschrieben. In pharmakokinetischen Studien mit radioaktiv markiertem Impfstoff wurden bis zu 21,5 Prozent der injizierten Dosis in der Leber und deutlich geringere Mengen in Milz, Nebennieren und Eierstöcken nachgewiesen.

In einigen Organen (Leber, Milz, Eierstöcke) also recht hohe Konzentrationen.
Bei Krebs-verursachenden Stoffen gilt der Satz des Paracelsus nicht.

2 Toxizität

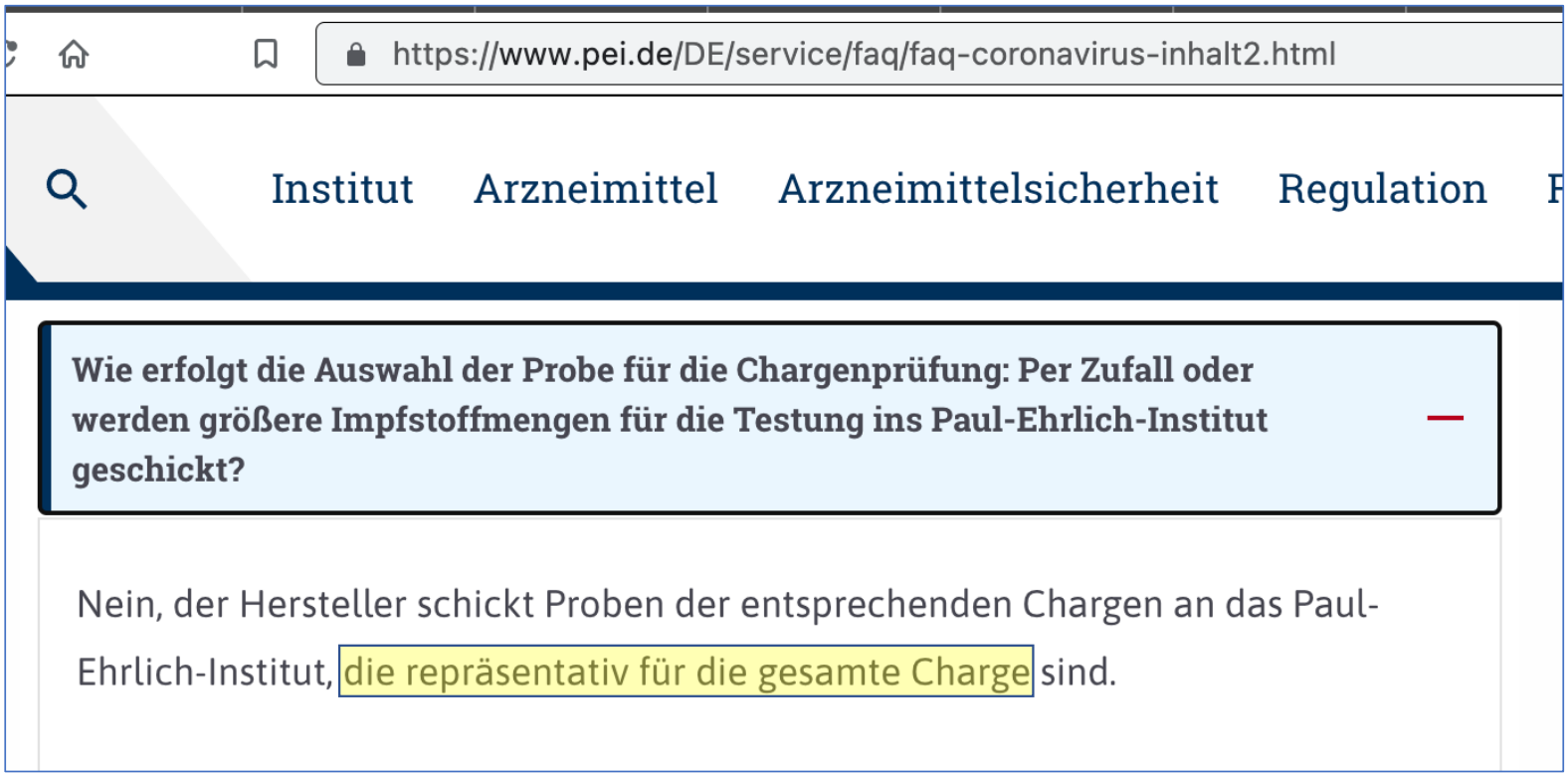
(a) Nanopartikel (gefährlich?)
(b) N^1-Methylpseudouridin (gefährlich?)
(c) Lipid ALC-315 (gefährlich?)
(d) DNA-Reste (Verunreinigung?)
(e) Spike-Proteine (Faktor 100.000)
(f) Sicherheitsdatenblatt (hohes toxisches Potential)
(g) Anreicherung in bestimmten Organen

1 Farbe

2 Toxizität

3 Qualitätskontrolle

3



So etwas verdient nicht den Namen „Qualitätskontrolle“.
„Repräsentativ für die gesamte Charge“: Natürlich kann man das nicht wissen.

Tab. P.5-1. des 'Rapporteur's Rolling Review assessment repo

Table P.5-1. BNT162b2 drug product specifications.

	Quality Attribute	Analytical Procedure[a]	Acceptance Criteria
	Composition and Strength		
1	Appearance	Appearance (Visual)	White to off-white suspension
1	Appearance (Visible Particulates)	Appearance (Particles)[b]	Essentially free from visible particulates
	Subvisible Particles	Subvisible Particulate Matter[b, c]	Particles ≥10 µm: ≤6000 per container[b,c]
			Particles ≥ 25 µm: ≤600 per container[b,c]
	pH	Potentiometry[b]	6.9 – 7.9
	Osmolality	Osmometry[b, d, e]	425 - 625 mOsmol/kg
	LNP Size	Dynamic Light Scattering (DLS)	40 to 180 nm
	LNP Polydispersity	Dynamic Light Scattering (DLS)	≤ 0.3
	RNA Encapsulation	Fluorescence assay	≥ 80%
	RNA content	Fluorescence assay	0.50 ± 0.13 mg/mL
	ALC-0315 content	HPLC-CAD	4.50 to 9.25 mg/mL
	ALC-0159 content	HPLC-CAD	0.55 to 1.20 mg/mL
	DSPC content	HPLC-CAD	0.90 to 2.05 mg/mL
	Cholesterol content	HPLC-CAD	1.80 to 3.90 mg/mL
	Container content for injections	Volume of injections in containers[e, f]	Not less than the sum of the nominal volumes of 5 doses
	Identity		
	Lipid identities	HPLC-CAD[e]	Retention times consistent with references (ALC-0315, ALC-0159, Cholesterol, DSPC)
2	Identity of encoded RNA sequence	RT-PCR[e]	Identity confirmed
	Potency		
	In Vitro Expression	Cell-based flow cytometry	≥ 30% Cells Positive
	Purity		
3	RNA Integrity	Capillary Gel Electrophoresis	≥ 50% intact RNA
	Adventitious Agents		
	Bacterial Endotoxin	Endotoxin (LAL)[b]	≤ 12.5 EU/mL
	Sterility	Sterility[b]	No Growth Detected
	Container Closure Integrity	Dye incursion[g]	Pass

a. All assays performed on stability unless otherwise noted.
b. Compendial
c. USP<787> (obscuration method), and aligned with upcoming (Jan 2021) revision of Ph. Eur. 2.9.19
d. USP<785>; also in accordance with Ph Eur. 2.2.35, with minor difference in instrument calibration
e. Assay not performed on stability.
f. Procedure is aligned with Test for Extractable Volume of Parenteral Preparations.
g. Tested at release and on stability for stability batches only
Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; FACS = fluorescence activated cell sorter; ddPCR = droplet digital PCR; qPCR = quantitative PCR; dsRNA = double stranded RNA; LAL = Limulus amebocyte lysate; EU = endotoxin unit

Nur vier Tests beim PEI!

Ungeeigneter Test.

Dr. W. sagte vor dem BVerwG, dass die pH-Messung das 4. Experiment sei, es ist aber die *in-vitro*-Expression des Spike-Proteins („Wirksamkeit" = „potency").

Identität:
Stand der Technik: *Next-generation sequencer*
Etwas richtige RNA reicht.
Etwa 4000 Basen: welche werden getestet?

Wirksamkeit:
Statt doppel-blinder randomisierter kontrollierter Studie (RCT)

Reinheit:
50% intakte RNA ist genug!
Nicht-intakte RNA ist auch aktiv!

Kein Test auf DNA-Verunreinigungen.

Tab. P.5-1. des 'Rapporteur's Rolling Review assessment repo

Table P.5-1. BNT162b2 drug product specifications.

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Purity		
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Adventitious Agents		
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Sterility	Sterility[b]	No Growth Detected
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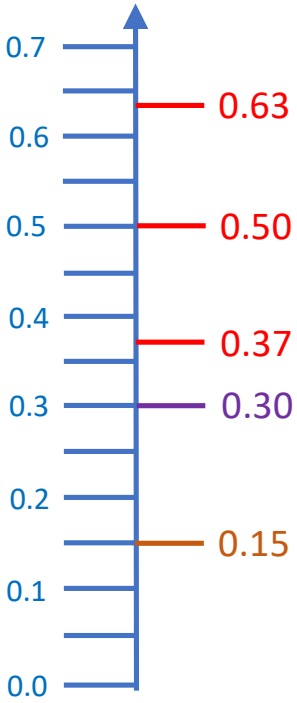
Fantastische Toleranzen

pH-Wert: Faktor 10!

LNP-Size: Gegen Rat der EMA-Experten

Gesamte Zusammensetzung:
Darf auch das Doppelte sein!

3



0.15 **x 4.2** = 0.63

Konzentration intakte & verkapselte mRNA [mg/mL]

▪ ***Table P.5-1. BNT162b2 drug product specifications.*** (unverdünnt)

Quality Attribute	Analytical Procedure[a]	Acceptance Criteria
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Potency		
In Vitro Expression	Cell-based flow cytometry	≥ 30% Cells Positive
Purity		
RNA Integrity	Capillary Gel Electrophoresis	≥ 50% intact RNA
Adventitious Agents		
Bacterial Endotoxin	Endotoxin (LAL)[b]	≤ 12.5 EU/mL
Sterility	Sterility[b]	No Growth Detected
Container Closure Integrity	Dye incursion[g]	Pass

Fantastische Toleranzen! Wirkstoff-Konzentration

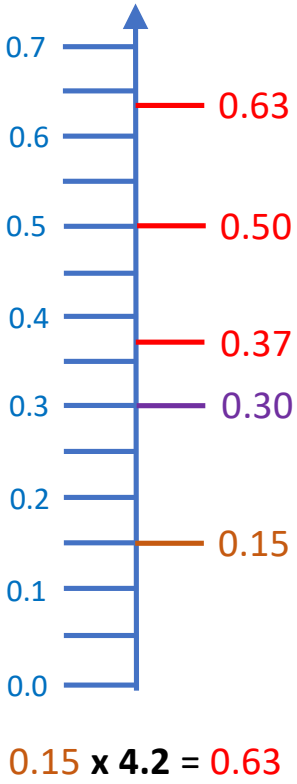
Verkapselte mRNA ≥ 80%

Konzentration mRNA ± 26%

Intakte mRNA ≥ 50%

Einzeldosis:
Menge mRNA zwischen 9.6 µg - 36 µg
(ohne Volumenfehler)
Und: wieviel Spike-Protein wird eigentlich gebildet?

3



0.15 **x 4.2** = 0.63

Konzentration intakte & verkapselte mRNA [mg/mL]

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Sterility	Sterility[b]	No Growth Detected
Container Closure Integrity	Dye incursion[g]	Pass

Fantastische Toleranzen!
Wirkstoff-Konzentration

Zum Vergleich: Eine einzelne Aspirin-500-mg-Tablette darf zwischen 475 mg und 525 mg Aspirin enthalten (95 bis 105%):
475 **x 1.1** = 525.

3 Qualitätskontrolle

- Probe per „Pizzataxi“ statt kontrollierter Probenahme.
- Nur 4 Tests.
- Test 1 (optische Erscheinung): sinnlos.
- Test 2 (Identität): Eine Spur reicht.
- Test 3 (Integrität): 50% mit dem richtigen Molekülgewicht sind genug.
- Test 4 (Wirksamkeit): Reagenzglas statt randomisierter kontrollierter Studie.
- Einzeldosis: Menge mRNA zwischen 9.6 µg - 36 µg (Faktor 4)
- Alle anderen Konzentrationen 100 oder 200%!
- pH-Wert variiert um eine dekadische Einheit (Faktor 10)!
- LNP-Größe: 40-180 nm!

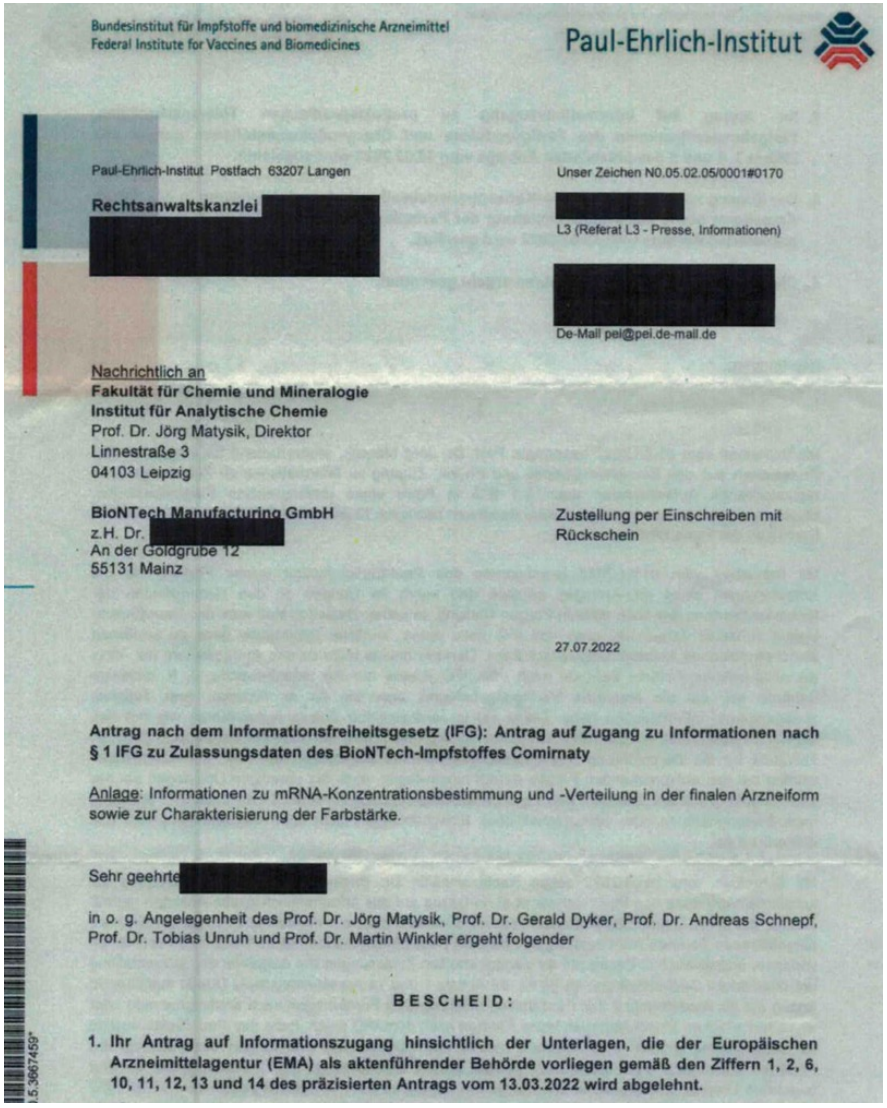
1 Farbe

2 Toxizität

3 Qualitätskontrolle

Nachtrag

Transparenz: Das **PEI verweigert** uns die Einsicht in die Prüfprotokolle



Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut Postfach 63207 Langen

Unser Zeichen N0.05.02.05/0001#0170

Rechtsanwaltskanzlei [redacted]

[redacted]

L3 (Referat L3 - Presse, Informationen)

[redacted]

De-Mail pei@pei.de-mail.de

Nachrichtlich an
Fakultät für Chemie und Mineralogie
Institut für Analytische Chemie
Prof. Dr. Jörg Matysik, Direktor
Linnestraße 3
04103 Leipzig

BioNTech Manufacturing GmbH
z.H. Dr. [redacted]
An der Goldgrube 12
55131 Mainz

Zustellung per Einschreiben mit Rückschein

27.07.2022

Antrag nach dem Informationsfreiheitsgesetz (IFG): Antrag auf Zugang zu Informationen nach § 1 IFG zu Zulassungsdaten des BioNTech-Impfstoffes Comirnaty

Anlage: Informationen zu mRNA-Konzentrationsbestimmung und -Verteilung in der finalen Arzneiform sowie zur Charakterisierung der Farbstärke.

Sehr geehrte [redacted]

in o. g. Angelegenheit des Prof. Dr. Jörg Matysik, Prof. Dr. Gerald Dyker, Prof. Dr. Andreas Schnepf, Prof. Dr. Tobias Unruh und Prof. Dr. Martin Winkler ergeht folgender

BESCHEID:

1. Ihr Antrag auf Informationszugang hinsichtlich der Unterlagen, die der Europäischen Arzneimittelagentur (EMA) als aktenführender Behörde vorliegen gemäß den Ziffern 1, 2, 6, 10, 11, 12, 13 und 14 des präzisierten Antrags vom 13.03.2022 wird abgelehnt.

März 2023

VERWALTUNGSGERICHT DARMSTADT

BESCHLUSS

In dem Verwaltungsstreitverfahren

des Herrn Prof. Dr. rer. nat. Jörg Matysik,
[redacted]

Kläger,

bevollmächtigt:

Rechtsanwältin Dr[redacted]
Z[redacted]en,
- Prof. Dr. Matysik / PEI -

gegen

die Bundesrepublik Deutschland, vertreten durch das Paul-Ehrlich-Institut, Bundesamt für Sera und Impfstoffe, - Rechtsreferat -,
Paul-Ehrlich-Straße 51 - 59, 63225 Langen,
- N0.05.02.05/0001#0170 -

Beklagte,

wegen Verfahren nach dem Informationsfreiheitsgesetz

Transparenz: Die **EMA verweigert** alle wesentlichen Zahlen

BNT162b2
3.2.S.4.3 Validation of Analytical Procedures
Quantitative Polymerase Chain Reaction (qPCR)

3.2.S.4.3. QUANTITATIVE POLYMERASE CHAIN REACTION (qPCR)

3.2.S.4.3.1. Overview

The qPCR analytical procedure for the determination of residual DNA template content has been validated for BNT162b2 drug substance (DS) in conformance with ICH Q2(R1) guidelines.

This section references the validation and transfer report numbers that detail the testing, experimental design, method evaluation, acceptance criteria and results for the validation and transfer of the analytical procedure. The type of validation, involved sites, and references to the validation and transfer reports are provided in Table 3.2.S.4.3-1.

Table 3.2.S.4.3-1. BNT162b2 Drug Substance method Validation and Transfer Reports for qPCR

Validation or Transfer	Site(s)	Report
Co-validation	4.2 1st ind	VAL100146017 Report for the Validation of Test Method TM100010388 - Quantitation of Residual DNA Template (4.2 1st ind) in PF-07305885 Drug Substance Using qPCR Technology
Validation		MVR-20-0007-qPCR and MVR-21-0006-V01-qPCR
Transfer		RPT-140496: Transfer Report for Drug Substance Quantitative Polymerase-Chain Reaction (qPCR) Assay 4.2 1st ind
4.2 1st ind		

BNT162b2
3.2.S.4.3 Validation of Analytical Procedures
Reversed Phase - High Performance Liquid Chromatography (RP-HPLC)

3.2.S.4.3. REVERSED PHASE-HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (RP-HPLC)

The RP-HPLC analytical procedure is validated 4.2 1st ind as a quantitative procedure for the determination of the 5'-cap content in BNT162b2 drug substance (DS) and includes assessments of precision (repeatability, intermediate precision and reproducibility), accuracy, specificity, linearity, quantitation limit, range and robustness. The validation results are provided in Table 3.2.S.4.3-1. The RP-HPLC analytical procedure for determining the 5'-cap content in DS is validated for its intended use.

Table 3.2.S.4.3-1. Validation Characteristics, Experimental Design, Acceptance Criteria and Results

Validation Parameter	Experimental Design	Acceptance Criteria	Validation Results
Precision – Repeatability (System)	Six injections from a single preparation of DS (5'-capped RPA of), tested by 1 analyst at 4.2 1st ind	4.2 1st ind	
Precision – Repeatability (Method)	Triplicate DS sample preparations at 3 levels (RPA of 4.2 1st ind (n=9), tested by 1 analyst at 4.2 1st . The overall precision, calculated from the normalized values, was reported.		
Intermediate Precision	4.2 1st ind		
Reproducibility			

Transparenz

Ich frage mich als **Zeuge**:

Könnte der UA des Sächsischen Landtags die ungeschwärzten Chargen-Prüfprotokolle des PEI anfordern?

Könnte der UA des Sächsischen Landtags die ungeschwärzten Zulassungsdokumente der EMA (*common technical dossier*) anfordern?

„Die freiwillige Einwilligung der **Versuchsperson** ist unbedingt erforderlich“
Nürnberger Kodex (1945/46)

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Nürnberger Kodex (1945/46)

Sage das als Zeuge:
Informierte Einwilligung (engl. *informed consent*) des Patienten wäre nötig gewesen.
Grundvertrauen vieler Bürger ist erschüttert.
Offene & ehrliche Aufarbeitung ist nötig!

Danke für Ihre freundliche Aufmerksamkeit!

1986&87 mit Aktion Sühnezeichen/Friedensdienste: Freiwilligendienst im Pflegeheim „Beth Achwa“ in Tel Aviv–Yad Eliahu