

Chargendifferenzen in der Tödlichkeit

Absicht, Dummheit oder schlichtweg ein Qualitätsproblem?


Dr. Sabine C. Stebel

RESEARCH LETTER

WILEY

Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine

Die Hypothese

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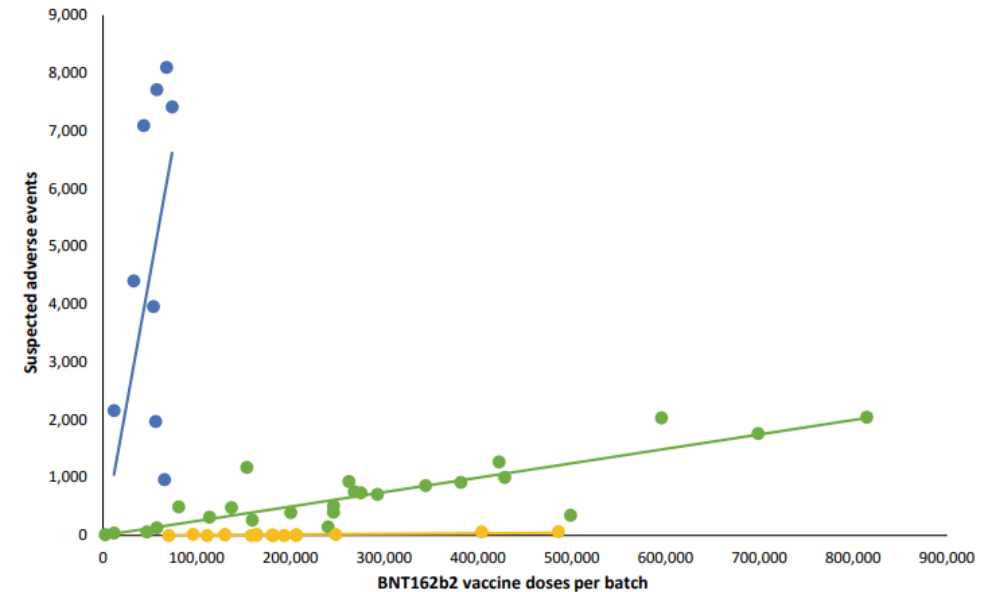
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FIGURE 1 Numbers of suspected adverse events (SAEs) after BNT162b2 mRNA vaccination in Denmark (27 December 2020–11 January 2022) according to the number of doses per vaccine batch. Each dot represents a single vaccine batch. Trendlines are linear regression lines. Blue: $R^2 = 0.78$, $\beta = 0.0898$ (95% confidence interval [CI] 0.0514–0.1281), green: $R^2 = 0.89$, $\beta = 0.0025$ (95% CI 0.0021–0.0029), yellow: $R^2 = 0.68$, $\beta = 0.000087$ (95% CI 0.000056–0.000118). Vaccine batches representing the blue, green and yellow trendlines comprised 4.22%, 63.69% and 32.09% of all vaccine doses, respectively, with 70.78%, 27.49% and 47.15% (blue trendline), 28.84%, 71.50% and 51.99% (green trendline), and 0.38%, 1.01%, and 0.86% (yellow trendline) of all SAEs, serious SAEs, and SAE-related deaths, respectively.

The Biomolecular Corona of Lipid Nanoparticles for Gene Therapy

Valentina Francia*, Raymond M. Schiffelers, Pieter R. Cullis, and Dominik Witzigmann*

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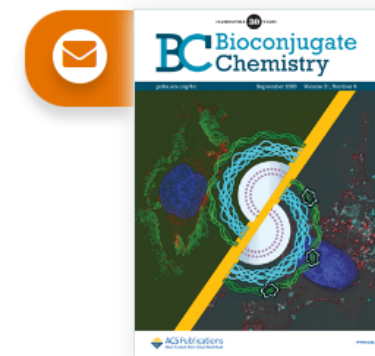
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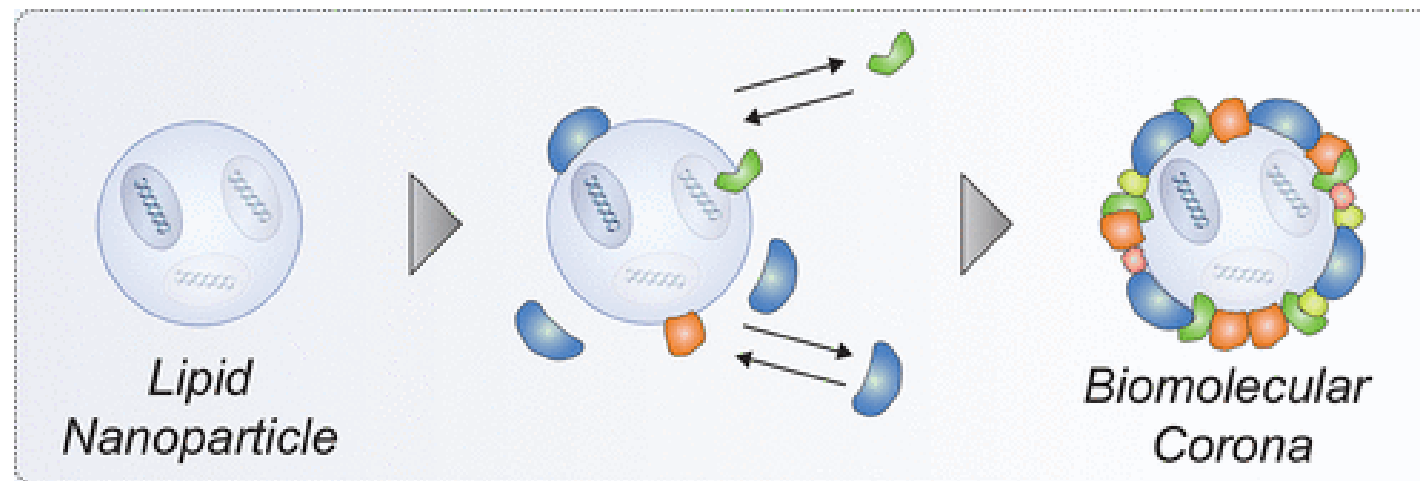
Bioconjugate Chemistry

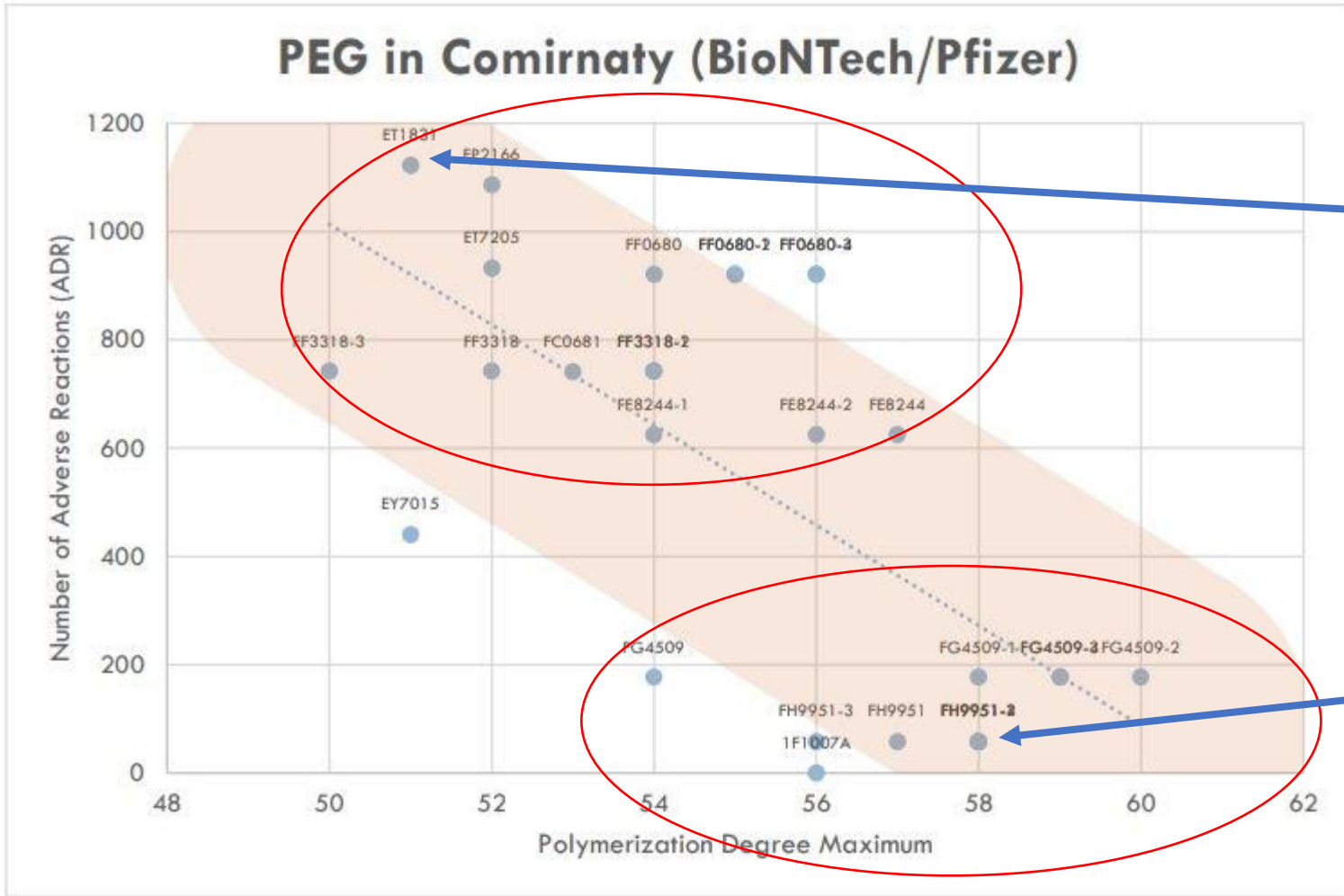
nanoparticles, Peptides and proteins, Targeting

<https://pubs.acs.org/doi/10.1021/acs.bioconjchem.0c00366>

DE: *Nicht nur das Vorhandensein von PEG, sondern auch **seine Länge** und Oberflächendichte sind für die Erreichung seiner (der Coronas) Funktion entscheidend.*

Corona = erwartbarer Grenzflächeneffekt





Je länger der PEG- Schwanz,
desto geringer die Nebenwirkung

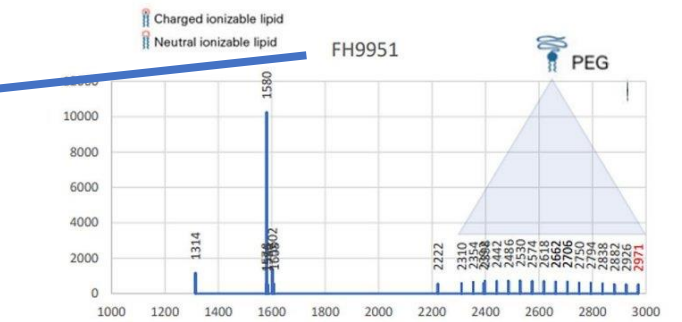
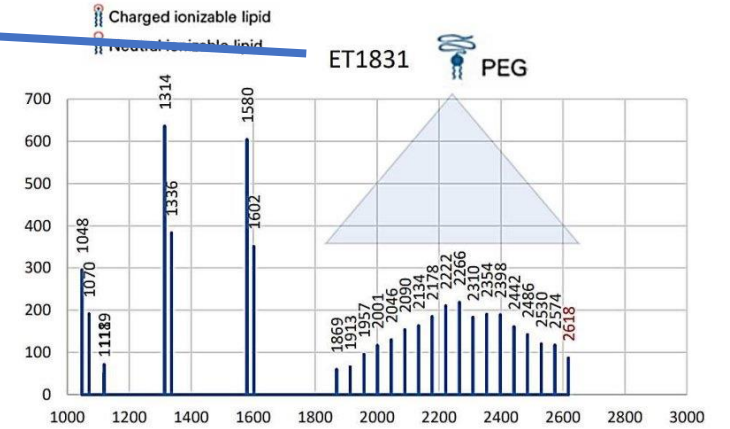


Figure 7: From the mass spectra of samples from different batches of Comirnaty vaccine (BioNTech/Pfizer), the maximum chain lengths were compared with the number of reported vaccination complications. A clear correlation can be seen. The blue dots are associated with the BioNTech/Pfizer batch numbers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

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?

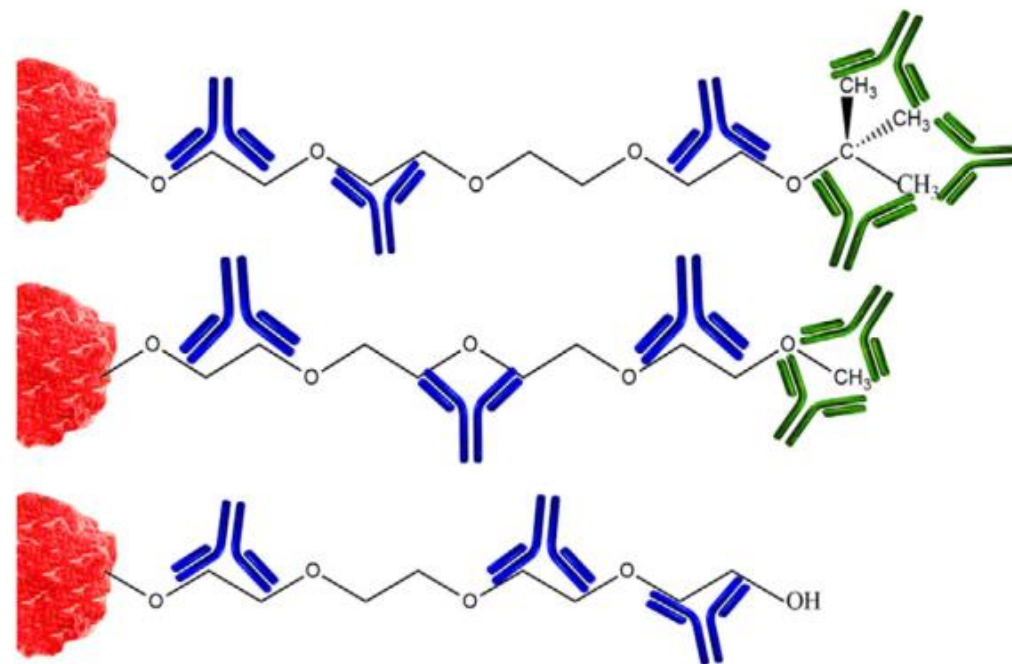
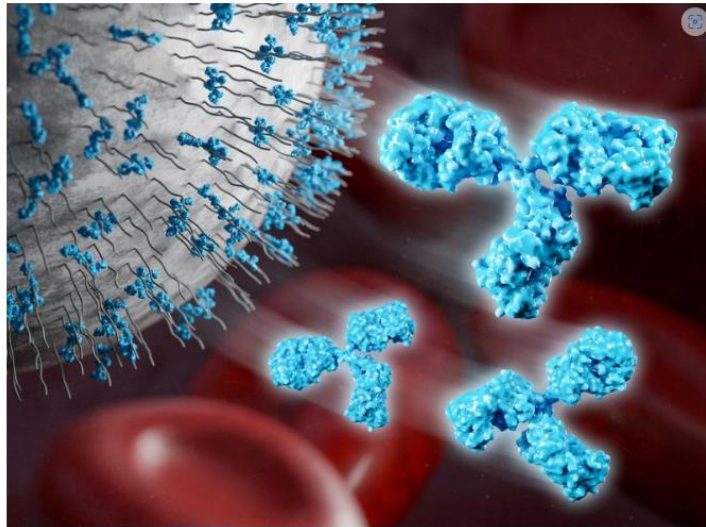


Figure 1. Schematic representation of different anti-PEG antibodies. The blue immunoglobulin is directed versus the backbone of the polymer, while the green antibodies are specific for the end-group. The picture shows that the immunogenicity of PEG is directly related to the hydrophobicity of the end-chain.

Molekulare Abwehrkräfte: Studie zeigt Antikörper gegen Polyethylenglykol bei 83 Prozent der deutschen Bevölkerung



Anti-PEG Antikörper zirkulieren im Blut vieler Menschen und binden an PEGylierte Nanoträger | Download

<https://nachrichten.idw-online.de/2023/10/20/molekulare-abwehrkraefte-studie-zeigt-antikoerper-gegen-polyethylenglykol-bei-83-prozent-der-deutschen-bevoelkerung>

Issue 10, 2023

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From the journal:
Nanoscale Horizons

Anti-PEG antibodies enriched in the protein corona of PEGylated nanocarriers impact the cell uptake†



[Mareike F. S. Deuker](#),^a [Volker Mailänder](#),^{ba} [Svenja Morsbach](#) ^{*a} and [Katharina Landfester](#) ^a

 [Author affiliations](#)

Deuker MFS, Mailänder V, Morsbach S, Landfester K. Anti-PEG antibodies enriched in the protein corona of PEGylated nanocarriers impact the cell uptake. *Nanoscale Horiz.* 2023 Sep 26;8(10):1377-1385. doi: 10.1039/d3nh00198a. PMID: 37591816. <https://pubmed.ncbi.nlm.nih.gov/37591816/>



Seven of Nine, MD
@53v3n0fn1n3

... <https://twitter.com/53v3n0fn1n3/status/1713446963536965738>

Thats why its so interesting, that the first autopsy of a breakthrough case had exactly the predicted liver changes, but no positive PCR.

pubmed.ncbi.nlm.nih.gov/33872783/

Arne did find liver pathology but not always spike expression. LIVER is major "immune" organ. Acute phase metabolism.

[Post übersetzen](#)



Seven of Nine, MD @53v3n0fn1n3 · 1 Std.

In 2021-2022 I have treated some liver tox myself. Skin not so much.

Even the care home death report in the corona comittee was full of major liver symptoms: dizziness up to coma, itchy skin up to yellowish colouring. Stomach pain only if organ swollen. Decolouring of poo.

1

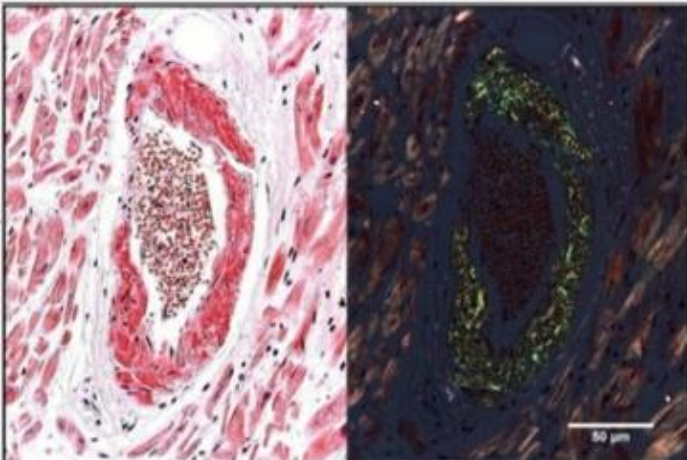


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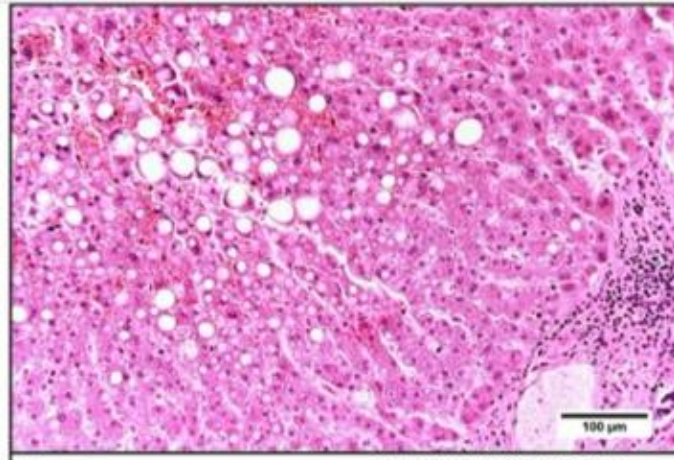


13. Juni 2021



Myocardium:
Hypertrophy, Amyloidosis

SARS-CoV2 RT-PCR:
positive (Ct 32.2)



Liver:
Steatosis, Sinus dilatation

SARS-CoV2 RT-PCR:
negative

sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) (PEG-DSPE) with Tween 20 containing short (C11) PEG alkyl chain [155]. The authors found that the usage of the short PEG alkyl chain led to a significantly improved lymph node targeting after intramuscular administration in mice [155]. Few studies focused on actively targeting of lymphocytes. Ramishetti et al. functionalized the LNP surface by anti-CD4 monoclonal antibody to target CD4⁺ T cells [156]. Veira et al. have used an ASSET (Anchored Secondary sEvy Enabling) thus improving the effectiveness of LNP-siRNA drug [150]. This study is in agreement with the previous study by Judge et al. where the authors found less formed anti-PEG antibodies and a substantial reduction of side effects upon repetitive dosing in mice when PEGylated liposomes containing a shorter alkyl chain (C14) PEG-lipid versus a longer alkyl chain C16 PEG-lipid were used [151]. Studies directly examining the effects of anti-PEG antibodies on the efficacy and safety of LNP-mRNA drugs containing PEG lipids are

Vlatkovic I. Non-Immunotherapy Application of LNP-mRNA: Maximizing Efficacy and Safety. *Biomedicines*. 2021 May 10;9(5):530. doi: 10.3390/biomedicines9050530. PMID: 34068715; PMCID: PMC8151051. <https://pubmed.ncbi.nlm.nih.gov/34068715/>

=== Zulieferer für Nanolipide ===

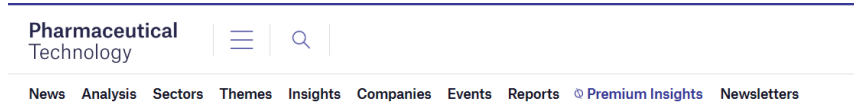
1. **Croda** = Avanti (haben Avanti aus "Project Lightspeed" 2020 gekauft)
2. **Merck** ab Februar 2021 zusätzlich ab 2022 mit seiner im Februar 2022 für 750-780 Millionen USD gekauften Firma Exelead
3. **Evonik** ab April 2021



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Croda supports Pfizer-BioNTech COVID-19 vaccine

Avanti, a company we acquired in 2020, has a strong track record in supplying R&D quantities of lipid-based drug delivery technologies to pharmaceutical companies including those developing mRNA drugs. When the COVID-19 pandemic hit, mRNA vaccine candidates were fast-tracked to Phase II clinical trials and Avanti became a key supplier. Due to increased demand, Avanti needed to ramp up its R&D capability and lipid production capacity quickly.



News |

Merck and BioNTech to boost lipid supply for Covid-19 vaccine production

Merck and BioNTech have announced a further expansion of their strategic partnership to accelerate the supply of urgently needed lipids and boost the amount of their delivery by the year-end.

February 8, 2021



Produkte & Lösungen

PRODUKTIONS-START IN REKORDZEIT: EVONIK LIEFERT ERSTE LIPIDE AUS DEUTSCHER PRODUKTION AN BIONTECH

Evonik beschleunigt die Produktion des COVID-19-Impfstoffs von Pfizer-BioNTech: Monate früher als geplant liefert Evonik die dringend benötigten Lipide für den mRNA-basierten Impfstoff an BioNTech.

In nur acht Wochen hatten Spezialisten am Standort Hanau die Lipid-Produktion aufgebaut, die die hohen Qualitätsanforderungen erfüllt. Zunächst war der Lieferstart für Mitte des Jahres vorgesehen.

„Die Produktion in dieser Geschwindigkeit aufzubauen, ist eine großartige Leistung“, sagt Evonik-Chef

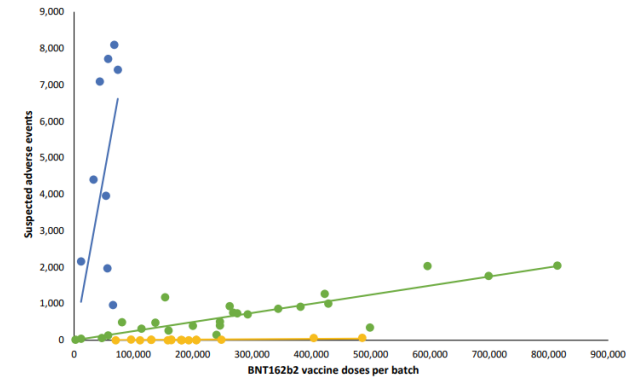


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LONG READ

Reflections on Covid-19 inbound supply chain issues

Covid-19 has had a significant impact throughout the biopharmaceutical industry, not least on the inbound supply chain, which has been hit by issues such as restricted supplies, the need for new sourcing strategies and how to design and build new facilities.

Specific comments said that delays in supply change notifications are often too late to plan for, that **suppliers and biomanufacturers may have different standards in quality systems, and there is a need for proactive communication about changes.** “Interactions are unlikely to ever be classed as optimal and so will be an ongoing need,” said **Bob Brooks, BioPhorum Supply Partner Leader.** “But the survey shows the strength of feeling at the current time and that people understand that more work needs to be done in this space.”

<https://www.biophorum.com/reflections-on-covid-19-inbound-supply-chain-issues/>

4. The Participating Member State acknowledges that the Vaccine and materials related to the Vaccine, and their components and constituent materials are being rapidly developed due to the emergency circumstances of the COVID-19 pandemic and will continue to be studied after provision of the Vaccine to the Participating Member States under the PA. The Participating Member State further acknowledges that the long-term effects and efficacy of the Vaccine are not currently known and that there may be adverse effects of the Vaccine that are not currently known. Further, to the extent applicable, the Participating Member State acknowledges that the Vaccine shall **not be serialized.**

Wie konnte das passieren?

Das sind die Folgen, wenn man nicht serialisiert.

*„Der teilnehmende Mitgliedsstaat erkennt an, dass der Impfstoff und die mit dem Impfstoff zusammenhängenden Materialien sowie ihre Komponenten und Bestandteile aufgrund der Notsituation der COVID-19-Pandemie rasch entwickelt und nach der Bereitstellung des Impfstoffs an die teilnehmenden Mitgliedstaaten im Rahmen des APA weiter untersucht werden. Der teilnehmende Mitgliedsstaat erkennt ferner an, dass die langfristigen Auswirkungen und die Wirksamkeit des Impfstoffs derzeit nicht bekannt sind und dass der Impfstoff unerwünschte Wirkungen haben kann, die derzeit nicht bekannt sind. Weiterhin, soweit anwendbar, erkennt der Teilnehmerstaat an, dass **der Impfstoff nicht in Serie produziert werden wird.**“*

- Absicht?
- Dummheit?
- Qualitätsproblem?