



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Commentary

All vials are not the same: Potential role of vaccine quality in vaccine adverse reactions



Yihua Bruce Yu*, Marc B. Taraban, Katharine T. Briggs

Bio- and Nano-Technology Center, University of Maryland School of Pharmacy, Baltimore, MD 21201, USA
 Institute for Bioscience and Biotechnology Research, 9600 Gudelsky Drive, Rockville, MD 20850, USA

1. Introduction

A recent commentary in this journal proposes looking beyond polyethylene glycols (PEG) when investigating anaphylactic reactions to mRNA COVID-19 vaccines [1]. It suggests examining other ingredients in those vaccines as potential causes of anaphylaxis. We agree with the need to broaden the scope when investigating vaccine adverse reactions, but we propose going beyond vaccine ingredients. A recent study reported that 581 people with anaphylaxis histories from previous vaccine shots did not develop anaphylaxis after receiving the Pfizer/BioNTech mRNA COVID-19 vaccine [2], suggesting that the vaccine ingredients might not always be the cause for anaphylaxis associated with this vaccine. While both active and inactive ingredients of a vaccine may be the cause of some adverse reactions, another possible cause to consider is sub-par quality of the individual vial.

We suggest taking the quality of individual vaccine vials into account in an adverse reaction investigation, i.e., a serious adverse reaction, anaphylaxis or other types, might be caused by one defective vial out of many good-quality vials. An argument for this possibility is that vaccine adverse reactions are not always reproducible on re-exposure [3], which hints at an element of chance. For example, a recent retrospective study found that 159 patients who had immediate reactions to the first dose of mRNA COVID-19 vaccines, including 19 individuals with anaphylaxis after the first-dose, tolerated the second dose [4]. The reason for this is unclear at this time. It is not inconceivable that the first and second doses may respectively involve vials of different quality, and therefore elicit different responses from a person. When the defect rate is low, it is highly unlikely that a given person will receive two bad doses in a row. For example, if the defect rate is 1 per 10^5 , the probability that a given person receiving two bad doses is 10^{-10} .

Indeed, focusing entirely on vaccine ingredients in adverse reaction investigations may leave an investigation unsolved when good-quality ingredients are not the cause. In Sweden, high counts of narcolepsy were noticed after immunization with Pandemrix (an H1N1 influenza vaccine) in 2009 [5]. Investigations that

focused on the adjuvant in Pandemrix failed to establish a causal link between narcolepsy and the adjuvant [6]. To this date, the cause has not been identified [7]. The culprit might have been a few defective vials in the batch delivered exclusively to Sweden rather than the adjuvant or other ingredients. Collecting quality data on every vial before injection might have prevented those narcolepsy incidents, but such a practice is not currently in place. In fact, the current quality control system for vaccines is not well equipped to catch a few defective vials among many good-quality ones unless the defects are visible to human eyes.

In this commentary, we introduce an emerging noninvasive inspection technology—water proton nuclear magnetic resonance (wNMR)—that could be used for fast and reliable quantitative inspection of sealed and labelled vials of liquid drug products. wNMR could be used to quantitatively inspect every vial before product release at the production site, before injection at the vaccination site, and anywhere in between. We discuss vials in this commentary, but other primary containers for liquid drug products such as syringes, pens, bottles, etc., could also be inspected by wNMR.

2. The current system for vaccine quality control

Quality control (QC) for vaccines and drugs is conducted at the batch level, not at the individual vial level. Specifically, extensive quantitative testing is conducted at each and every step of vaccine manufacturing, up to the point of the purified bulk drug substance (DS). The DS then goes through the fill-finish unit operations to become the drug product (DP), i.e., the sealed and labelled vials ready for distribution. At the DP level, not all vials in a batch are tested quantitatively because testing requires opening sealed vials and drawing out the content for analysis. Once a vial is opened or punctured, its integrity is compromised and therefore is no longer suited for release. Consequently, quantitative invasive testing is performed only on a small fraction of finished vials in each batch, a process called statistical sampling.

The current QC system collects data on *none* of the released vials. Therefore, the quality of released vials is inferred from the quality of the few randomly selected vials opened and tested at the production site [8]. Such a QC system operates on the premise that all vials in a batch are the same, or sufficiently alike, when

* Corresponding author.

E-mail address: byu@rx.umaryland.edu (Y. Bruce Yu).

manufactured and remain the same all the way to injection. But *all vials are not the same* due to manufacturing and handling variabilities. Many factors, starting from the fill-finish unit operations and throughout the distribution process, may affect product quality at the individual vial level, and these could be overlooked in batch-level QC.

3. All vials are not the same due to manufacturing and handling variabilities

3.1. Manufacturing variability

No two objects can be made identical, be they two light bulbs, two cars, or two vials of a vaccine; there is always some object-to-object variability. Of course, variability does not necessarily mean defective products; it depends on the type and extent of variability. Pharmaceutical manufacturing, in general, is not very precise, at a level of 2–3 σ , with 2 σ quality corresponding to 308,537 defects per 10⁶ opportunities [9]. The precision for vaccine manufacturing may be even less than 2–3 σ because vaccine manufacturing is more complex than most pharmaceuticals, rendering manufacturing errors more likely. With this level of manufacturing precision, it is up to the QC system to detect and remove defective intermediates and final products.

The current QC system is well-equipped to catch defects that occur before the fill-finish unit operations, but it may miss defects that occur at the fill-finish unit operations and beyond. Starting from the fill-finish unit operations, the quality of individual vials might diverge. For example, in 2013, a fill-finish error caused the insulin level in 0.14% insulin pens in multiple batches to deviate from the target value by up to $\pm 50\%$ [10]. There was at least one report of a serious adverse reaction associated with one of the recalled batches [11]. Four weeks later, 33 batches of 3.3 million insulin pens were recalled [10].

The frequency or degree of meeting the quality standards in manufacturing is often not measured, reported, or made publicly available [9]. It would be unrealistic to expect a zero defect rate for any vaccine or drug product. The smaller the defect rate, the more likely the defective vials will escape sampling-based QC and get released. The 0.14% error rate (1,400 per 10⁶) that occurred in the fill-finish unit operations of the insulin product is not very low but nonetheless evaded detection. However, if every insulin pen was quantitatively inspected before release using noninvasive analytical technologies, such as wNMR, individual pens with filling errors above a preset acceptable level could have been detected and removed from the batch [12].

3.2. Handling variability

Once deemed releasable by QC testing, a batch of vaccines will go through the distribution process to reach vaccination sites. For some vaccines, there are additional handling procedures right before injection. For example, both the Pfizer/BioNTech and the Moderna mRNA COVID-19 vaccines require thawing before injection, and the Pfizer/BioNTech vaccine further requires dilution after thawing. In mass vaccination programs, handling variability, including mishandling of various types, is hardly avoidable. The most extreme examples of COVID-19 vaccine mishandling include intentionally leaving vaccines outside the freezer in Wisconsin [13], and unintentionally vaccinating people with expired vaccines in New York [14]. Less extreme but much more common mishandling is cold chain breaches.

Most vaccines require cold chain for distribution. The regular cold chain is 2–8 °C. However, some vaccines require more stringent cold chains. For example, the Pfizer/BioNTech and Moderna

mRNA COVID-19 vaccines, respectively, require –70 °C and –20 °C for distribution. Cold chain breaches, in general, are not rare. In 2012, the Inspector General of the Department of Health and Human Services issued a report entitled “Vaccines for Children Program: Vulnerabilities in Vaccine Management” [15]. The report identified multiple vulnerabilities in the distribution of vaccines for children (VFC) in the United States. Key findings include that 76% of providers had exposed VFCs to inappropriate temperatures for at least 5 cumulative hours in a 2-week period. All 45 providers had recorded temperatures that differed from independently measured temperatures during the 2-week period. Another study published by industry scientists in 2018 also found that exposing vaccines to incorrect storage temperature is not rare in the US [16]. Cold chain breaches do not necessarily make a vaccine vial defective; it depends on the temperature and exposure duration. Although the U.S. has many checks in place, without quantitative inspection of individual vials before injection, it is impossible to know whether any vial has become defective.

In addition to cold chain breaches, other types of handling variability are also hard to avoid. Examples include agitation during transportation, exposure to sunlight during storage, duration of thawing, precision of dilution, etc. The cumulative effects of manufacturing and handling variabilities may lead to significant vial-to-vial variability at vaccination sites.

3.3. Vial-to-vial variability at vaccination sites

Manufacturing variability occurs before product release while handling variability occurs between product release and injection. These two variabilities combined may render the vaccine vials in a batch sufficiently different at vaccination sites, i.e., vial-to-vial variability. In our own work, we demonstrated the effectiveness of wNMR to detect freezing variability among vials from the same carton of aluminum-adjuvanted vaccines [17]. Of course, freezing variability may or may not translate into differences in safety and efficacy. The observation simply shows that vial-to-vial variability indeed exists.

A recent example of vial-to-vial variability is that 39 vials of the Moderna mRNA COVID-19 vaccine were found to contain foreign materials at multiple vaccination sites in Japan [18]. Three men died within days after receiving their second dose of the vaccine. On September 10, 2021, a Japanese Health Ministry panel stated that it does not have enough information to determine whether there is a causal link between the three deaths and the vaccine [19]. Moderna recalled three lots of the vaccine and issued a statement saying that the most probable cause of the foreign materials were a result of friction between two improperly aligned machinery components during manufacturing, and this caused stainless steel particulates to end up in some vials [20]. It appears, the affected vials were only distributed to Japan.

Fortunately, in this case, the foreign materials, millimeter in size, were large enough to be visible to the human eye so that they were caught at vaccination sites. But how they escaped pre-release visual inspection is puzzling. Moreover, not all defects are visible to the human eye. If visible defects can escape QC detection, the chance of subvisible defects escaping QC detection is likely even higher. Some subvisible defects, such as a wrong dose, might occur before product release, while other subvisible defects, such as fragmented or aggregated ingredients, might emerge after product release. Quantitative inspection of every vial before injection may help to catch defective vials and thereby prevent some adverse reactions.

If vial-to-vial variability indeed plays a role in vaccine adverse reactions, then the complexity of the distribution and handling procedures might affect the rate of adverse reactions. The rationale is that more complex procedures might lead to greater product

variability at vaccination sites. For the two mRNA COVID-19 vaccines, the anaphylactic reaction rate was 4.7 and 2.5 per 10^6 doses, respectively, for Pfizer/BioNTech and Moderna vaccines [1]. This might be due to ingredient differences between the two vaccines. But it is also possible that the higher anaphylactic rate of the Pfizer/BioNTech vaccine is due, at least in part, to its more stringent cold chain requirement ($-70\text{ }^\circ\text{C}$) and more complex handling procedure (dilution before injection). The fact that 19 people who developed anaphylaxis after the first dose of the mRNA COVID-19 vaccines could tolerate the second dose [4] also suggests that vial-to-vial variability might be at play. As mentioned earlier, probabilistically, it is unlikely that the same person would receive two bad doses in a row.

4. The case for vial-level QC

4.1. Defective products and sensitive populations together may result in adverse reactions

As discussed above, all vials are not the same; some might be defective. But not all defective vials will cause adverse reactions. Depending on the severity and nature of the defect, defective vials might only cause adverse reactions in some people (sensitive populations), but not in all people. In other words, adverse reactions to vaccines and drugs might be the result of both vial-specific and person-specific factors.

A prior occurrence of this type was during a clinical trial of the erythropoietin analog HX575 for treating anemia. Of the 174 participants receiving HX575, two developed neutralizing antibodies against erythropoietin, an endogenous glycoprotein. Of the two participants, one developed pure red cell aplasia and one died of myocardial infarction. The trial was terminated [21]. Later studies revealed that the adverse events were likely caused by a combination of participant and product variability [22]. Only some participants carried certain DNA alleles that caused them to be sensitive to protein aggregates, and the protein aggregates were only present in some of the pre-filled syringes of the drug. In fact, the variation of protein aggregate level in the syringes ranged from below the detection limit up to 5%. It appears that a few outlier syringes caused harm in a few sensitive individuals. This highlights the need for vial-level QC.

4.2. Random and latent occurrences of product defects are difficult to catch

The case of the erythropoietin analog HX575 is instructive in another way: it took over six months for the aggregates to reach detectable levels [23]. Hence the defect was not only random, i.e., varying from syringe to syringe, but also latent, i.e., emerging long after product release. Although this specific example is a therapeutic protein, there is no reason to preclude random and latent defects from happening to vaccines. In the absence of vial-level quality data at the point-of-care, severe adverse reactions caused by random and latent product defects are hard to prevent before injection and hard to investigate after injection.

4.3. Batch-level QC restricts vaccine adverse reaction investigations

Because there is no data on individual vials, the current paradigm in vaccine adverse reaction investigations is to treat people *individually* but vaccine vials *collectively*. Specifically, if person X is vaccinated with vial Y of vaccine Z and develops a serious adverse reaction, the investigation will examine the *specific biology* of person X and *commonalities of all vials* of vaccine Z, such as PEG in mRNA COVID-19 vaccines. The possibility that vial Y is defective

and thereby causes the adverse reaction is typically not considered because there is no data on vial Y.

Lack of data on individual vials forces the investigation to operate under the assumption that person X will develop an adverse reaction to vaccine Z no matter which vial is used. The investigation will then sample unused vials from the same batch; vial Y is left out of the investigation because it is already gone with no data on its quality left behind. If the sampled, unused vials from the same batch as vial Y were found to be of good quality, the investigation may then conclude that there is no evidence of causal link between the adverse reaction and the vaccine. Batch-level QC is not equipped to address directly whether a specific adverse reaction is caused by a defective vial of vaccine.

In essence, lack of vial-level quality data biases vaccine adverse reaction investigations towards the commonalities of all vials, such as the ingredients, and ignores the peculiarities of individual vials, such as defects. It is worth putting this bias into perspective. For the two mRNA COVID-19 vaccines, unless the defect rate of the Pfizer/BioNTech and Moderna vaccines at vaccination sites is known to be markedly lower than 4.7 and 2.5 per 10^6 , respectively, there is no *a priori* reason to ignore the possibility that the anaphylactic events were caused by defective vials. Focusing solely on commonalities of all vials may lead the investigation to a dead-end as it was in the above case of high counts of narcolepsy in Sweden after immunization with Pandemrix [5].

4.4. Recalls lead to massive vaccine wastage

When a few vials in a batch are found to be defective, often the entire batch cannot be used. Sometimes, additional batches are put aside out of precaution. One example is the Moderna mRNA COVID vaccine in Japan, where 39 vials in one lot were found to contain foreign materials. Not only was this lot recalled, but two other lots were also recalled. The reason is that the three lots were manufactured around the same time and on the same manufacturing line [18]. In total, 1.63 million doses were recalled because 39 vials were found defective. Such extreme precaution, although understandable, leads to a huge amount of wastage. It is possible that only a small fraction of vials in these lots are defective; the rest might be perfectly fine. For example, in the insulin pen recall, only 0.14% of pens had wrong doses [10]. The consequence was that 99.84% of 3.3 million pens ended up wasted. Vial-level data hold the potential to pinpoint which vial is defective and which is not, and thereby prevent such wastage.

5. Enhancing vaccine quality control through quantitative noninvasive inspection

At its core, the current paradigm in adverse reaction investigations, treating people *individually* but vaccine vials *collectively*, stems from our ability to collect quantitative data on every person, but inability to collect quantitative data on every vial. With no data on individual vials, one has no choice but to treat vaccine vials collectively; the decision to accept or reject vaccine vials is at the batch level, not at the vial level. In the case of severe adverse reactions, it is hard to draw definitive conclusions based on batch-level data. Without vial-level data, an element of guess and chance becomes unavoidable.

Our current inability to collect quality data on every vial is primarily because the analytical technologies for quality assessment are invasive; data collection compromises the DP integrity. To build a more robust QC system, noninvasive inspection technologies that maintain DP integrity are needed, i.e., technologies that can collect quantitative data on sealed and labelled vials without damaging the DS inside the vials. To collect data on millions and

even billions of vials at both manufacturing and vaccination sites, the technologies also need to be fast, affordable, robust, and easy to use.

These requirements constitute a tall order. Hence, it is worth pointing out what is *not* needed from the noninvasive inspection technologies. These technologies are used to detect DP defects that occur after the fill-finish unit operations, i.e., after the quality of the bulk drug substance has been assured by invasive analytical technologies. For finished vials, what is needed from such technologies is a quick accept/reject decision, with the criteria preset through prior validation/calibration using invasive technologies. There is no need for such noninvasive inspections to provide chemical and biological details when outlier vials are detected; those details can be provided by invasive analytical technologies on vials ‘flagged’ by noninvasive inspection technologies, which may take a long time.

6. Water proton NMR: An emerging noninvasive inspection technology

In wNMR, the signal source is from the water protons, like a medical MRI. However, unlike medical MRI, which involves large, expensive equipment and complex, time-consuming procedures, wNMR uses compact inexpensive equipment and simple procedures that take seconds in most cases. We have applied wNMR to noninvasively inspect marketed vaccines and insulin products [12,17,24]. wNMR is still at its early stages and it will take significant engineering efforts to make wNMR suited for inspecting millions to billions of vials. Of course, other noninvasive inspection technologies based on different principles may also be developed.

7. Path forward

Enhanced QC based on vial-level data may facilitate vaccination programs and help to overcome vaccine hesitancy. We are still a long way from collecting data on every vial of a vaccine. There are technical, financial, and regulatory issues to be resolved. The situation is somewhat analogous to taking the genetics or biomarkers of every person into account, which also has technical, financial, and regulatory issues. As we progress toward precision medicine and vaccination, the point-of-care collection of data on every person and every vial may eventually become the norm.

A potential starting point is a clinical trial that collects data on every vial before injection. By matching genetic and outcome data on every person with quality data on every vial, a better understanding on vaccine safety and efficacy might be achieved. While results from one clinical trial might not be generalizable to all vaccines, they nonetheless may demonstrate the benefit of inspecting every vial before injection and thereby can spur further development in noninvasive inspection technologies and their implementation.

For vaccine developers, collecting data on every vial before injection may help prevent giving trial participants subpar or even defective vaccines, which may improve trial success. For example, wNMR can readily detect aggregates in therapeutic protein formulations [25]. The clinical trial of the erythropoietin analog HX575 might have been saved had the protein aggregate level in every syringe been quantified before injection.

This commentary highlights the limitations of current vaccine quality control and adverse reaction investigations. Our intent is to raise awareness and spur development. We are not suggesting that vaccination programs be halted until quality data on every vial are collected. A society functions with what it has and progresses by recognizing and then overcoming its limitations. For vaccine QC and adverse reaction investigation, the starting point for

improvement, in our view, is recognizing gaps in our knowledge, be it a person’s biology or a vial’s quality, and then developing enabling technologies to bridge those gaps. For governments and international organizations, investment in enabling technologies for enhanced QC might help to alleviate vaccine hesitancy and could be an integral part of pandemic prevention and control strategy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yihua Bruce Yu reports financial support was provided by US Food and Drug Administration. Yihua Bruce Yu reports financial support was provided by National Institute for Innovation in Manufacturing Biopharmaceuticals. Yihua Bruce Yu has patents issued to University of Maryland Baltimore. Yihua Bruce Yu has patents pending to University of Maryland Baltimore. Marc B. Taraban has patents issued to University of Maryland Baltimore. Marc B. Taraban has patents pending to University of Maryland Baltimore. Katharine T. Briggs has patents pending to University of Maryland Baltimore.

Acknowledgement

Our research on vaccine manufacturing and quality control is supported by the FDA (75F40119C10104) and NIIMBL (PC2.2-077).

References

- [1] Hatziantoniu S, Maltezou HC, Tsakris A, Poland GA, Anastassopoulou C. Anaphylactic reactions to mRNA COVID-19 vaccines: A call for further study. *Vaccine* 2021;39(19):2605–7. <https://doi.org/10.1016/j.vaccine.2021.03.073>.
- [2] Myles IA, Vinciguerra JS, Premus RT. Specialist confirmed allergic reactions to COVID-19 mRNA vaccines at a mass vaccination site. *Vaccine* 2021;39(32):4404–6. <https://doi.org/10.1016/j.vaccine.2021.06.061>.
- [3] McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol* 2018;141(2):463–72. <https://doi.org/10.1016/j.jaci.2017.12.971>.
- [4] Krantz MS, Kwah JH, Stone CA, Phillips EJ, Ortega G, Banerji A, et al. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients with Immediate Reactions to the First Dose. *JAMA Intern Med* 2021. <https://doi.org/10.1001/jamainternmed.2021.3779>.
- [5] Sarkanen TO, Alakuijala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. *Sleep Med Rev* 2018;38:177–86. <https://doi.org/10.1016/j.smrv.2017.06.006>.
- [6] Weibel D, Sturkenboom M, Black S, de Ridder M, Dodd C, Bonhoeffer J, et al. Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines – Multi-country assessment. *Vaccine* 2018;36(41):6202–11. <https://doi.org/10.1016/j.vaccine.2018.08.008>.
- [7] Edwards K, Hanquet G, Black S, Mignot E, Jankosky C, Shimabukuro T, et al. Meeting report narcolepsy and pandemic influenza vaccination: What we know and what we need to know before the next pandemic? A report from the 2nd IABS meeting. *Biologicals* 2019;60:1–7. <https://doi.org/10.1016/j.biologicals.2019.05.005>.
- [8] Yu YB, Taraban MB, Wang W, Briggs KT. Improving Biopharmaceutical Safety through Verification-Based Quality Control. *Trends Biotechnol* 2017;35(12):1140–55. <https://doi.org/10.1016/j.tibtech.2017.08.010>.
- [9] Yu LX, Kopcha M. The future of pharmaceutical quality and the path to get there. *Int J Pharm* 2017;528:354–9.
- [10] European Medicines Agency. Batches of the Insulin Medicine NovoMix 30 FlexPen and Penfill to be recalled, (EMA/ 657469/ 2013) n.d. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/10/WC500153147.pdf.
- [11] US Food and Drug Administration. MAUDE Adverse Event Report: Novo Nordisk A/S Novopen Insulin Delivery Device 2013. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi_id=3621493.
- [12] Briggs KT, Taraban MB, Wang W, Yu YB. Nondestructive Quantitative Inspection of Drug Products Using Benchtop NMR Relaxometry—the Case of NovoMix® 30. *AAPS PharmSciTech* 2019;20:214. <https://doi.org/10.1208/s12249-019-1428-6>.
- [13] Stanley-Becker I, Salcedo A. Wisconsin pharmacist who ‘intentionally’ spoiled more than 500 vaccine doses is arrested, police say. *Washington Post* 2020. <https://www.washingtonpost.com/nation/2020/12/31/covid-vaccines-destroyed-wisconsin-hospital/>.
- [14] The Associated Press. Nearly 900 people got expired Covid-19 vaccine doses at site in New York’s Times Square. *NBC News* 2021. <https://www.nbcnews.com/>

- news/us-news/nearly-900-people-got-expired-covid-19-vaccine-doses-site-n1270983.
- [15] Levinson DR. Vaccines for Children Program: Vulnerabilities in Vaccine Management (OEI-04-10-00430) Office of Inspector General, Dept. of Health and Human Services; 2012.
- [16] Wilson E, Zhu C, Galea S, Marko A, Victoria Urdaneta V, Straus W. Turning up the heat: Effect of new vaccine for children's (VFC) program recommendations for use of temperature monitors upon incorrect product storage adverse event reporting. *Vaccine* 2018;36(12):1516–20.
- [17] Briggs Katharine T, Taraban Marc B, Yu Y Bruce. Quality assurance at the point-of-care: Noninvasively detecting vaccine freezing variability using water proton NMR. *Vaccine* 2020;38(31):4853–60. <https://doi.org/10.1016/j.vaccine.2020.05.049>.
- [18] Tsukimori O. Contaminated Moderna vaccines to have little impact on Japan's rollout, Suga says. *The Japan Times*; 2021.
- [19] Kyodo J. Japan so far unable to link deaths to withdrawn batches of Moderna vaccine. *Japan Times* 2021. <https://www.japantimes.co.jp/news/2021/09/10/national/moderna-deaths-findings/> [accessed September 10, 2021].
- [20] Moderna, Takeda. Joint Statement from Moderna and Takeda on the Investigation of Suspended Lots of Moderna's COVID-19 Vaccine in Japan 2021. <https://investors.modernatx.com/news-releases/news-release-details/joint-statement-moderna-and-takeda-investigation-suspended-lots> [accessed September 1, 2021].
- [21] Haag-Weber Marianne, Eckardt Kai-Uwe, Hörl Walter H, Roger Simon D, Vetter Andrea, Roth Karsten. Safety, immunogenicity and efficacy of subcutaneous biosimilar epoetin- α (HX575) in non-dialysis patients with renal anemia: A multi-center, randomized, double-blind study. *Clin Nephrol* 2012;77(01):8–17. <https://doi.org/10.5414/CN107304>.
- [22] Rubic-Schneider T, Kuwana M, Christen B, Aßenmacher M, Hainzl O, Zimmermann F, et al. T-cell assays confirm immunogenicity of tungsten-induced erythropoietin aggregates associated with pure red cell aplasia. *Blood Adv* 2017;1:367–79. <https://doi.org/10.1182/bloodadvances.2016001842>.
- [23] Seidl Andreas, Hainzl Otmar, Richter Marleen, Fischer Robert, Böhm Stephan, Deutel Britta, et al. Tungsten-induced denaturation and aggregation of epoetin alfa during primary packaging as a cause of immunogenicity. *Pharm Res* 2012;29(6):1454–67. <https://doi.org/10.1007/s11095-011-0621-4>.
- [24] Taraban MB, Wang Y, Briggs KT, Yu YB. Inspecting Insulin Products Using Water Proton NMR. I. Noninvasive vs. Invasive Inspection. *J Diabetes Sci Technol* 2021. <https://doi.org/10.1177/19322968211023806>, published online on June 11, 2021.
- [25] Taraban Marc B, DePaz Roberto A, Lobo Brian, Yu Y Bruce. Water proton NMR: a tool for protein aggregation characterization. *Anal Chem* 2017;89(10):5494–502. <https://doi.org/10.1021/acs.analchem.7b00464>. <https://doi.org/10.1021/acs.analchem.7b00464.s001>.