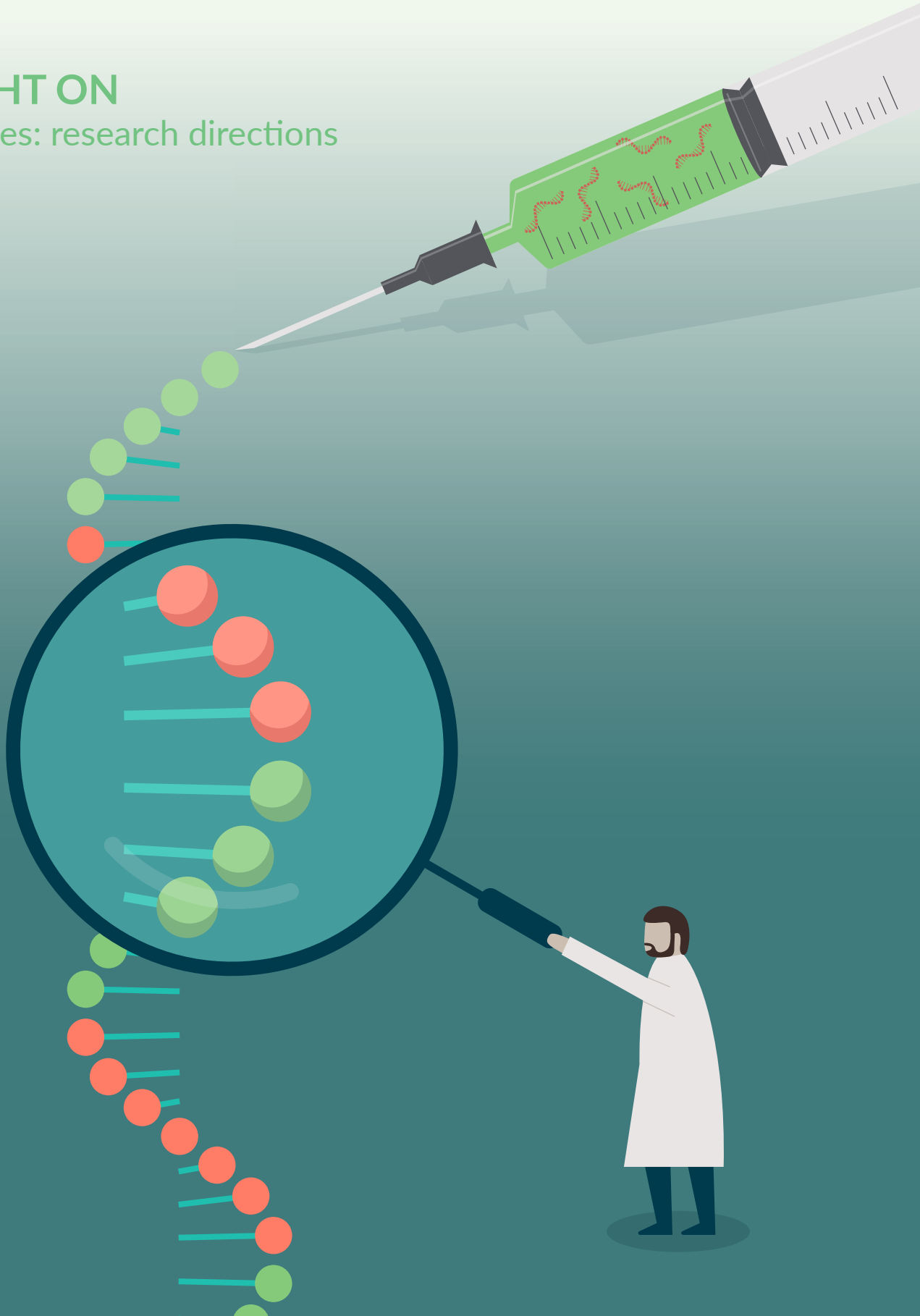
MAY 2024

Volume 3, Issue 3

VACCINE INSIGHTS

SPOTLIGHT ON

RNA vaccines: research directions



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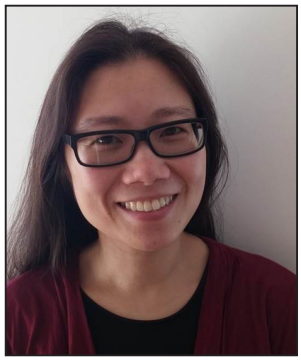

Charlotte Barker, Commissioning Editor, *Vaccine Insights*, speaks with **Ka-Wai Wan**, Senior Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency, about pandemic preparedness, the regulatory pathway for mRNA-based vaccines, and the opportunities and challenges posed by their rapid evolution.

Vaccine Insights 2024; 3(3), 97–105

DOI: 10.18609/vac.2024.019

Q What are you working on currently in the vaccine space?

KWW: Currently, I am working on several vaccine applications, both initial submissions and variations encompassing biological and chemical products. Additionally, I am preparing for scientific and regulatory advisory meetings and addressing queries from external stakeholders and internal colleagues.

Apart from these routine tasks, I am involved in developing a 'decision tree' to assist researchers in navigating the regulatory aspects of nanomedicines. Further, there is ongoing discussion regarding the platform approach for mRNA-LNP products, although these documents are still in the early stage of development.

Q What is your experience to date with the evaluation of the mRNA-LNP products?

KWW: I have an academic background in nanomedicine research and have been involved in evaluating mRNA-LNP applications since the onset of the pandemic in 2020. Over the past few years within the agency, we have thoroughly assessed both initial applications and subsequent variations. It is important to note that prior to the emergence of mRNA-LNP COVID-19 vaccines, we had extensive experience, spanning over two decades, with other lipid-based nano drug delivery systems like liposomes.

Liposomes, such as those used in liposomal doxorubicin (Caelyx®), and the mRNA-LNP COVID-19 vaccines are both categorized as lipid-based nano-drug delivery systems, yet their structural and physiochemical attributes differ. It is important to emphasize this point as some may assume equivalence between liposomes and lipid nanoparticles in the context of mRNA vaccines; however, they are distinct entities.

Q Looking back at the COVID-19 pandemic, what have we learned about getting safe and effective vaccines to market as quickly as possible, especially in an emergency?

KWW: In an emergency situation, we must leverage existing knowledge among researchers, manufacturers, and regulators to act quickly. Prompt activation and concerted effort are essential to reach our shared objective swiftly, a challenge that we faced during the pandemic.

There are several requirements for responding effectively to a pandemic. Firstly, resources, both human and financial, must be maximized to enable accelerated development of the critical medicines and medical devices needed to save lives. Our primary goal during the COVID-19 pandemic was to minimize the number of casualties, necessitating the pooling of expertise across various domains to support vaccines and medical device development, particularly at the peak of the pandemic.

Pulling together resources from various organizations to collaborate towards a common goal was critical in expediting the vaccine development process. In my opinion, the collective pooling of manpower and substantial funding allocated to support COVID-19 research significantly accelerated development efforts and deepened the understanding of the disease, its epidemiology, targets, and genome sequencing.

Secondly, capacity building—identifying the best options to increase manufacturing capacity and ensuring manufacturers have the correct knowledge for quick and successful production. Numerous labs, clinical testing centers, and manufacturing sites were established to boost production capabilities. Sharing knowledge and expertise was essential to maximize capacity as isolated efforts would not have been sufficient. Rapid distribution of critical information enabled this quick decision-making.

"During the pandemic, communication and information sharing were significantly enhanced, surpassing previous standards."

Thirdly, effective communication and information sharing are key, involving seamless communication among researchers, manufacturers, organizations, and regulators. During the pandemic, communication and information sharing were significantly enhanced, surpassing previous standards. Viral genome sequences were promptly uploaded to global databases, allowing researchers from different labs to quickly identify potential targets to develop mRNA- or protein-based vaccines.

Another critical point, and a key lesson learned, is the importance of communication with the general population, both to identify clinical trial participants and subsequently explain the benefits and associated risks of a new vaccine. Acknowledging that not all aspects are entirely beneficial and understanding and weighing the risks against the benefits, as with any medication, is crucial. This transparency is key to building trust with the general public.

During the pandemic, anti-vaccine misinformation, particularly on social media, posed a significant challenge. Addressing the resulting skepticism was essential to ensure sufficient global vaccine coverage. Outreach efforts were necessary to engage with skeptics, providing transparent explanations of the benefits and risks associated with vaccination. Tailoring information to individual needs and concerns was vital in fostering understanding and acceptance.

Additionally, leveraging digital platforms proved invaluable. The public's use of symptom-tracking apps fostered engagement and understanding of COVID-19's impact on the community. Engaging with the public through digital platforms helped improve their understanding of both the products and disease progression in general.

Finally, ensuring efficient vaccine distribution to diverse populations is a key requirement for an effective emergency response. One of the major challenges of expediting the COVID-19 vaccines was handling the ultra-cold supply chain required for certain vaccines, ensuring efficient distribution, and maintaining proper storage and administration conditions. Given the availability of multiple vaccine options, it was crucial to disseminate adequate information to healthcare professionals administering the vaccines. This process was tightly controlled to ensure appropriate actions were taken at each step, ultimately reaching the intended population.

Q What regulatory actions were most impactful during the pandemic?

KWW: The rolling review process, despite being labor-intensive, proved necessary in accelerating vaccine assessments during the pandemic. Manufacturers could submit data as soon as it became available, allowing for continuous assessment of different data sets and providing necessary feedback in real time. The rolling review process supported daily discussions required to identify any gaps with manufacturers. Additionally, streamlining clinical trial

studies across multiple centers worldwide also accelerated the generation of clinical data and the pharmacovigilance system played a pivotal role in continuously monitoring and ensuring the safe and effective use of vaccines.

Frequent dialog between manufacturers and regulatory agencies worldwide was significant in keeping stakeholders updated on vaccine progress. This open discussion among regulatory authorities facilitated the consideration of vaccine dossiers. Assessors from different regulatory authorities were able to share the evaluation and identify any critical issues associated with vaccine applications, highlighting the benefits of a more streamlined and collaborative approach to assessment.

The Medicines and Healthcare Products Regulatory Agency (MHRA) had plans in place for a pandemic situation, allowing for the swift implementation of those plans when needed. Going forward, many mechanisms established during the pandemic are being retained and improved upon, becoming embedded in our system.

In the event of another pandemic, having these mechanisms already in place will enable a more efficient response. Lessons learned from experiences such as the rolling review process and the use of online meetings have demonstrated their effectiveness in working with companies and facilitating global communication across different time zones.

Further, existing collaborative programs such as ACCESS programs with international partners like Health Canada, TGA, and Health Singapore Authority, as well as initiatives like Project Orbis, were already in place pre-pandemic and have been further developed in light of recent experiences. These collaborative efforts are expected to continue and evolve, contributing to a more robust response in future health crises.

Overall, collective efforts contributed to achieving the common goal of minimizing COVID-19-related deaths. Sharing information among researchers, manufacturers, regulatory authorities, and the public, along with the mechanisms of communication between organizations, was key in vaccine development. Sustaining transparency and open dialogues is equally vital in the post-pandemic world.

Q What are the biggest potential pitfalls for companies seeking regulatory approval for a new mRNA-LNP product and how should these be addressed?

KWW: All applications are required to meet the necessary standards for quality, safety, and efficacy, regardless of any expedited processes. Some manufacturers may assume that having a licensed product with a similar technology could fast-track the approval of a new product using the same technology or delivery system. However, while previous data can inform the development of a new product, it is essential to generate product-specific information for the new product and ensure that proposed processes and controls are suitable.

Characterization of the new product, especially if changes have been made in the manufacturing processes or storage conditions, is crucial for consistency and meeting the required

standards. Relying solely on another product to justify the control specifications may not be appropriate if the boundaries are irrelevant or too broad.

Controls based on the available batch analysis data, processing data, and stability results have to be assessed before an application can be accepted. Sufficient data should be available to justify the proposed controls and the processes, and many of these are drug substance or product-specific, rather than copy-pasting without modifications. This holds true for both new entrants and established companies in the field. Compliance with regulatory guidances, such as those provided by ICH and WHO, is essential, regardless of the type of medicinal product being developed.

For platform terminology, it is important to define terms clearly as different companies may use different definitions. Dialog with manufacturers to align relevant data and submission requirements is crucial for effective communication and regulatory assessment.

Q The EMA has proposed creating a guideline on quality aspects for mRNA vaccines. Would you agree that this is an area where more guidance is needed?

KWW: Guidance documents are helpful as a way to support manufacturers and developers in navigating the complexities of product development. For mRNA-LNP vaccines, which contain both the mRNA and the lipid nanocarrier delivery system, comprehensive guidance is especially valuable due to the inherent complexity of these systems. Highlighting past issues and areas needing further investigation can help developers address potential challenges effectively.

It is worth noting that the WHO has already published a guidance document, which the MHRA contributed to during the drafting stage [1]. This document, released early in the pandemic, provided valuable information on the quality, safety, and efficacy of mRNA vaccines for the prevention of infectious diseases.

Additionally, the MHRA's active participation in initiatives such as the European Directorate for the Quality of Medicines and HealthCare (EDQM) mRNA vaccines working party and ACCESS consortium etc. allows for ongoing contribution to the development of guidance documents tailored to the specific needs of the industry. The upcoming guidance documents are expected to offer further insights and direction into the industry, facilitating the development of new mRNA vaccines.

Q What future guidelines or regulatory evolution relating to mRNA products would you like to see?

KWW: The question of how to expand the use of mRNA products beyond COVID-19 vaccines is a hot topic; however, there should be a differentiation between vaccines for

infectious diseases and cancer immunotherapy. While mRNA vaccines have been authorized solely for COVID-19 thus far, there is potential for their applications in various other conditions, including chronic diseases.

In future, there may be a broader range of mRNA products targeting diverse diseases. Cancer immunotherapy, specifically cancer vaccines (though not strictly vaccines from a regulatory standpoint), are personalized and unique to each patient. Providing information on developing these therapies with robust data sets, whether for individual treatments or off-the-shelf options, could be valuable given the increasing interest.

Additionally, there is a need for an excipient master file, similar to active substance master files, specifically for novel excipients being used in LNPs for mRNA vaccine delivery. This would streamline the assessment process by consolidating information on chemical synthesis, controls, and stability for these excipients. While applying these excipients for different routes of administration may still require further nonclinical studies, having standardized excipient master files could optimize resource utilization and accelerate the assessment process.

Establishing standards for each excipient and eventually developing a database for widely used novel excipients could further enhance regulatory efficiency and ensure consistency in product evaluation. While this may take some time, it is a direction worth considering.

Q Are there any areas of regulatory divergence regarding mRNA products where greater international regulatory harmony would be beneficial?

KWW: When discussing mRNA products, it is important to consider the classification of these products within the regulatory framework. While mRNA vaccines are considered as biological products, the classification of chemical or biological products and the definition of gene therapy medicinal products may require updating or alignment to accommodate advancements in mRNA technology.

Currently, smaller RNAs such as siRNAs are typically considered chemical products due to their purely synthetic nature. However, as mRNA becomes more synthetically produced, utilizing cell-free systems without biological components like plasmid, questions arise about whether they should still be classified as biological products.

According to regulatory definitions, biological products typically involve substances produced or extracted from a biological source, necessitating specific testing and product controls. While mRNA has some similarities to shorter oligonucleotides like siRNAs, its greater complexity and size warrant advanced characterization tools to ensure structural integrity, morphology, and interactions with drug delivery systems. These are then more similar to biological products than to a well-defined chemical product.

Given that mRNA vaccines fall under the category of immunological medicinal products, it may be appropriate for them to be classified as biological products. However, as mRNA

"With advancements in cell-free production technology, there may be a future where mRNA will be entirely synthetically produced."

production transitions away from plasmids towards cell-free systems, updates to the definition may be necessary to accurately reflect the nature of these products.

Q What do you anticipate will be future trends in licensing new vaccines and mRNA technology?

KWW: Cell-free manufacturing is a key area to consider. Currently, plasmid DNA serves as the starting material for manufacturing mRNA via *in vitro* transcription method. Essentially, this involves using the plasmid. With advancements in cell-free production technology, there may be a future where mRNA will be entirely synthetically produced. This raises the challenge of defining what constitutes a biological product. The current definition specifies that the product is extracted from a biological source, so if mRNA is synthetically produced, this may need to be re-assessed.

This blurring of the line between chemical and biological products is becoming more frequent across the pharmaceutical space. Many medicinal products now target molecular mechanisms of action, interacting with mRNA, ribosomes, or cellular components. If these interactions occur within the intracellular compartment to activate activity, their classifications may also need to be considered, especially with advancements like circular and self-amplifying RNA.

For example, a recent paper published by CEPI discusses a system that contains two RNA fragments—one encoding the antigen and the other encoding the replicase. Unlike self-amplifying RNA, where the antigen and replicase are combined, this system uses two separate fragments. I understand that CEPI is currently supporting projects like these, termed 'trans-amplifying mRNA vaccines'.

The versatility of mRNA technology suggests there will be an increase in more multivalent mRNA vaccines combining COVID, influenza, and other vaccines where multiple strains or combinations are required. In addition, from a drug delivery perspective, advancements in lipid nanoparticles are making delivery systems more sophisticated. In future, targeted delivery systems may direct products to specific cellular compartments or cell types.

Despite these developments, the required standards for quality, safety, and efficacy of medicinal products remain unchanged. Assessments will still follow the same rigorous protocols, though the process may become more complex.

Q How will the International Recognition Procedure (IRP) introduced this year affect the approval of new medicines and vaccines, including mRNA-LNP products?

KWW: As of January 1, 2024, the EC Decision Reliance Procedure (ECDRP) has been replaced by the new International Recognition Procedure (IRP). The Mutual Recognition/Decentralized Reliance Procedure has been incorporated under the umbrella of IRP. Essentially, it is a continuation of the assessment process, albeit under a different framework.

The major difference is that it enables us to evaluate applications that have already been authorized by a specified Reference Regulator. All relevant documents must be provided to streamline this evaluation. Previously, with the ECDRP, companies could rely on the positive opinions and assessments from the Committee for Medicinal Products for Human Use (CHMP) at the EMA for our national applications. The IRP now expands this opportunity to include other Reference Regulators such as the Therapeutic Goods Administration, Health Canada, Swissmedic, and the FDA. It is important to understand that authorization in another country does not automatically translate to approval in the UK. We must still assess the benefits and risks for the UK population since the product will be used here. This is why there are different recognition routes categorized as type A and type B.

When the dossier is of high quality, with well-constructed submissions for modules 3, 4, and 5 as well as comprehensive product information, the IRP can accelerate the assessment process and benefit patients, especially for drugs targeting hard-to-treat conditions.

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BIOGRAPHY

KA-WAI WAN is a pharmacist by training and graduated from The UCL School of Pharmacy, London, UK. She was trained as a hospital pharmacist before completing her PhD in nanomedicine for protein and gene delivery at the Welsh School of Pharmacy, Cardiff, UK. Ka-Wai worked as an academic for over a decade and she was a Principal Lecturer in Pharmaceutics and Course Leader for the MSc Industrial Pharmaceutics prior to her transition to the Medicines and Healthcare products Regulatory Agency (MHRA) as a pharmaceutical assessor. She now leads on the assessment of nano-based medicinal products and provides regulatory and scientific advice on generic and innovative medicines, particularly on nanomaterials used for both small and macromolecules delivery. This includes nano-based drug delivery systems using polymers, liposomes and various types of lipid nanoparticles for a wide variety of medical applications, including mRNA-LNP products.

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Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has received support for attending the mRNA Therapeutics European Summit 2024. She is also on the boards of: the British Standards Institution/Nanotechnology Standardization Committee (BSI/NT1); the International Pharmaceutical Regulators Programme (IPRP) Nanomedicine Working Group; the EDQM mRNA Vaccines Working Party; the EDQM Nano Working Party; and the RPSGB Science and Research Committee.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

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Article source: Invited.

Interview conducted: Mar 14, 2024; **Revised manuscript received:** May 9, 2024;

Publication date: May 22, 2024.

VACCINE INSIGHTS

RNA VACCINES: RESEARCH DIRECTIONS

SPOTLIGHT

Swiss regulatory aspects and evaluation considerations for ATMPs and other nucleic acid-based products such as mRNA-based vaccines

Julia Djonova
Swissmedic

"Swissmedic is taking various measures to respond to innovation in order to provide appropriate support for developers and meet the expectations of industry and patient..."

VIEWPOINT

Vaccine Insights 2024; 3(3), 91–95

DOI: 10.18609/vac.2024.018

This brief overview presents the regulatory landscape for advanced therapy medicinal products (ATMPs) and other nucleic acid-based products in Switzerland and how Swissmedic is balancing innovation and safety with a flexible approach.

ATMPs and other nucleic acid-based products are complex, both from the regulatory and the scientific viewpoint. In Switzerland, a risk-based approach to the regulation and assessment of ATMPs—including mRNA vaccines—applies in order to take account of their particularities and potentially unknown risks. The goal is to ensure fast access to potentially curative medicines for conditions that had no treatment options until now, while ensuring optimal patient protection. With these two drivers in mind, the Swiss national authorization and supervisory authority for drugs and medical products, Swissmedic, is on the way to applying new strategies to respond to growing needs in the field of innovative medicine.

Regardless of the international legal specificities, ATMPs are widely considered potential game changers, with the potential to change the quality of life of patients with genetic and neurodegenerative diseases, and malignancies, amongst others. Swissmedic is taking various measures to respond to innovation in order to provide appropriate support for developers and meet the expectations of industry and patients for innovative treatment solutions.

The legal basis for all therapeutic products in Switzerland is provided by the Therapeutic Products Act [1]. In addition, for ATMPs and other nucleic acid-based products, the Transplantation Act [2], the Human Research Act [3], and the associated ordinances [4–6] are relevant. The Swiss regulatory agencies follow the definition of the EU legislation [7] and consider ATMPs as gene therapy products, cell therapy products, and tissue engineering products. On the other hand, based on the Release Ordinance [5], which is binding for Switzerland, products with defined nucleic acid sequences such as mRNA, oligonucleotides, siRNA, CRISPR gRNA, etc. are legally equivalent to microorganisms (including GMOs) and fall under the term 'biologically active genetic material'. Therefore, gene therapy products and other nucleic acid-based products are regulated with the same regulatory process. In the EU, ATMPs do not include synthetically produced products and exclude vaccines against infectious diseases; in Switzerland, however, ATMPs and other nucleic acid-based products can be synthetically produced. Furthermore, nucleic acid-based products, such as mRNA vaccines against infectious diseases, are considered in an analogical way to gene therapy products. For more information, please consult 'The Regulation of Cell Therapy and Gene Therapy Products in Switzerland' [8].

This current Swiss classification approach allows the application of flexible methods for assessment and authorization procedures (such as the use of a case-by-case benefit–risk assessment, the recognition of new manufacturing platforms and flexible clinical trial designs, the use of real-world data as supportive evidence [9], etc.) that consider the product in all its complexity and are applicable as a general rule for ATMPs and other nucleic acid-based products. Existing regulatory procedures such as accelerated assessment (fast track procedures) and conditional marketing authorization (such as post-authorization safety and efficacy studies) are also applicable. This regulatory flexible solution is essential to avoid any delays in the market launch or clinical trial authorization of those products by implementing specific scientific and regulatory instruments.

On the other hand and as a new strategy, Swissmedic has established an Innovation Office based on the Swiss Federal measures for the promotion of biomedical research and technology for the period until 2026. Its strategic objective is to ensure the optimum framework for biomedical research and technology in order to promote innovation and facilitate rapid access to safe and qualitative innovative therapies for patients. Due to the specificity of ATMPs and other nucleic acid-based products, the Innovation Office started with these products as a pilot project.

Although ATMPs and nucleic acid products have been heralded as potentially curative breakthrough medicines, to date, only a

limited number have been submitted worldwide for marketing authorization. This is due not only to the complexity of the products in terms of manufacturing and clinical trial criteria, but also the lack of regulatory experience among developers and start-ups, which are often located in a university, small company or spin-off (incubator) of a university. As they need assistance to align with the regulatory framework, Swissmedic uses different tools to support them such as an increased presence of Swissmedic's ATMP experts in the major research centers, and strengthening of early scientific advice meetings covering the entire process from GMP, through clinical trials, up to marketing authorization. In 2023, 37 on-site meetings and 34 clarification or pre-submission meetings were held, in which both regulatory and scientific issues were addressed. This very important early exchange of information helps to prevent incomplete submissions or the initiation of preclinical or clinical trials that do not meet the regulatory requirements. In this way, innovative projects can be accelerated.

Despite being defined as an independent group, ATMPs and nucleic acid products are by no means homogeneous in terms of their mode of action and biology. Due to their novelty, complexity, and technical characteristics, they are subject to specifically tailored requirements. For some of them, adjustments are necessary, such as the scope of the analytical, preclinical, and clinical data to demonstrate quality, safety, and efficacy. In order to deal with these complex aspects, these products are managed by a special division at Swissmedic as a central point for all ATMP topics. With its multidisciplinary experts, the ATMP division covers the entire life cycle from the planning of a production facility, a GMP/GDP/GCP inspection, clinical studies, authorization, and post-authorization market surveillance.

Finally, an active exchange is maintained with international authorities such as ICH, IPRP, EDQM, and ACCESS. It is important that regulatory authorities are aware of the positions and approaches of other regulatory authorities in the aim of harmonizing requirements. A scientific and regulatory convergence is important to provide public reassurance and support developers in that they can expect comparable assessment of their dossiers by different authorities.

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BIOGRAPHY

JULIA DJONOVA is Head of the Advanced Therapy Medicinal Products (ATMP) department at Swissmedic, the Swiss Agency for Therapeutic Products. Dr Djonova is a medical doctor with clinical experience in cardiology. She worked in research and teaching at the Swiss universities of Lausanne and Fribourg. Before starting in 2002 at Swissmedic, first as a clinical reviewer, inspector and then as head of the ATMP department, she worked for 3 years at the Federal Office of Public Health where she was actively involved in launching and establishing inspections activities with transplants, as well as the hemovigilance system in Switzerland. Dr Djonova is a representative in various national and international forums in the fields of cells/tissue engineering products and innovative therapies. She participates in the development of legal requirements and national and international guidelines in the area of advanced therapy products and represents the ATMP's pilot project within the Swissmedic Innovation's office. Dr Djonova is the Swiss representative expert in different international forums, for example International Conference of Harmonization (ICH), European Directorate for the Quality of Medicine (EDQM) for the field of Tissues, Cells and Organs, Cell Therapy Working Group (IPRF), Pharmaceutical Inspection Convention (PIC's), ACCESS, etc.

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Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has no conflicts of interest.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

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Article source: Invited.

Revised manuscript received: May 1, 2024; **Publication date:** May 15, 2024.

VACCINE INSIGHTS

RNA VACCINES: RESEARCH DIRECTIONS

SPOTLIGHT

Understanding vaccine hesitancy: a call for more social science in RNA vaccine research

Heidi J Larson
London School of Hygiene and University of Washington

"We need to use the time we have before the launch of new mRNA vaccines and therapeutics to build trust and confidence..."

VIEWPOINT

Vaccine Insights 2024;3(3),107–111

DOI: 10.18609/vac.2024.020

Although mRNA research has been ongoing for decades [1,2], when the mRNA vaccines were introduced in 2020 to protect against COVID-19, it was the first time there was such widespread public attention to mRNA globally. Hailed as one of the key means to mitigate the spread and serious impacts of the COVID-19 pandemic, the novelty of the mRNA vaccines combined with emergency authorization to allow quicker access to the

new vaccines, also made it particularly vulnerable to public anxiety. One study in nine countries demonstrated a clear link between the perceived novelty of the mRNA vaccine and levels of vaccine hesitancy, but also showed that as more and more people are vaccinated, generating positive peer influence, hesitancy can decline [3].

While new vaccines typically prompt more questions than routine, familiar ones, during the COVID-19 period these concerns combined with wider feelings of mistrust triggered by the handling of the pandemic, prompting the spread of rumors and misinformation. While some of the misinformation is correctable [4] and may mitigate hesitancy, in order to address other factors driving vaccine hesitancy—such as issues around trust and distrust or cultural or religious influences—we need social scientists to be part of the growing teams of researchers and opportunities around mRNA vaccines and therapeutics [5].

In late 2023, a new initiative called the Global Listening Project [6] interviewed over 70,000 people across 70 countries about their experiences during the COVID-19 crisis. Questions included overall levels of trust in government, the health system and health professionals, trusted information sources, key influencers, and future outlook, as well as perceptions of importance, safety and effectiveness of vaccines in general, and COVID-19 vaccines specifically.

One of the threads of questioning in the 70-country study was around perceptions of mRNA and willingness to accept a new mRNA vaccine if approved. The survey found great disparities across and within countries—from a high of 87% of respondents in Sierra Leone reporting they would take a new mRNA vaccine if approved, to a low of only 37% of respondents in South Africa (see Figure 1).

In response to another question asked in the same survey: 'Before today, how much, if at all, had you heard of vaccines or medicines that use messenger RNA (mRNA)?', 46% of Americans reported having heard a great deal or fair amount, with women and people over 55 years old less likely to have heard a lot about mRNA. In a related study conducted by the Global Listening Project in collaboration with Premise [7], surveys conducted through social media asked participants if they had ever heard of mRNA, 42% of respondents in Côte d'Ivoire replied 'yes', while 40% in Kenya, 32% in Ghana, and 29% in Nigeria reported ever having heard of vaccines or medicines using mRNA.

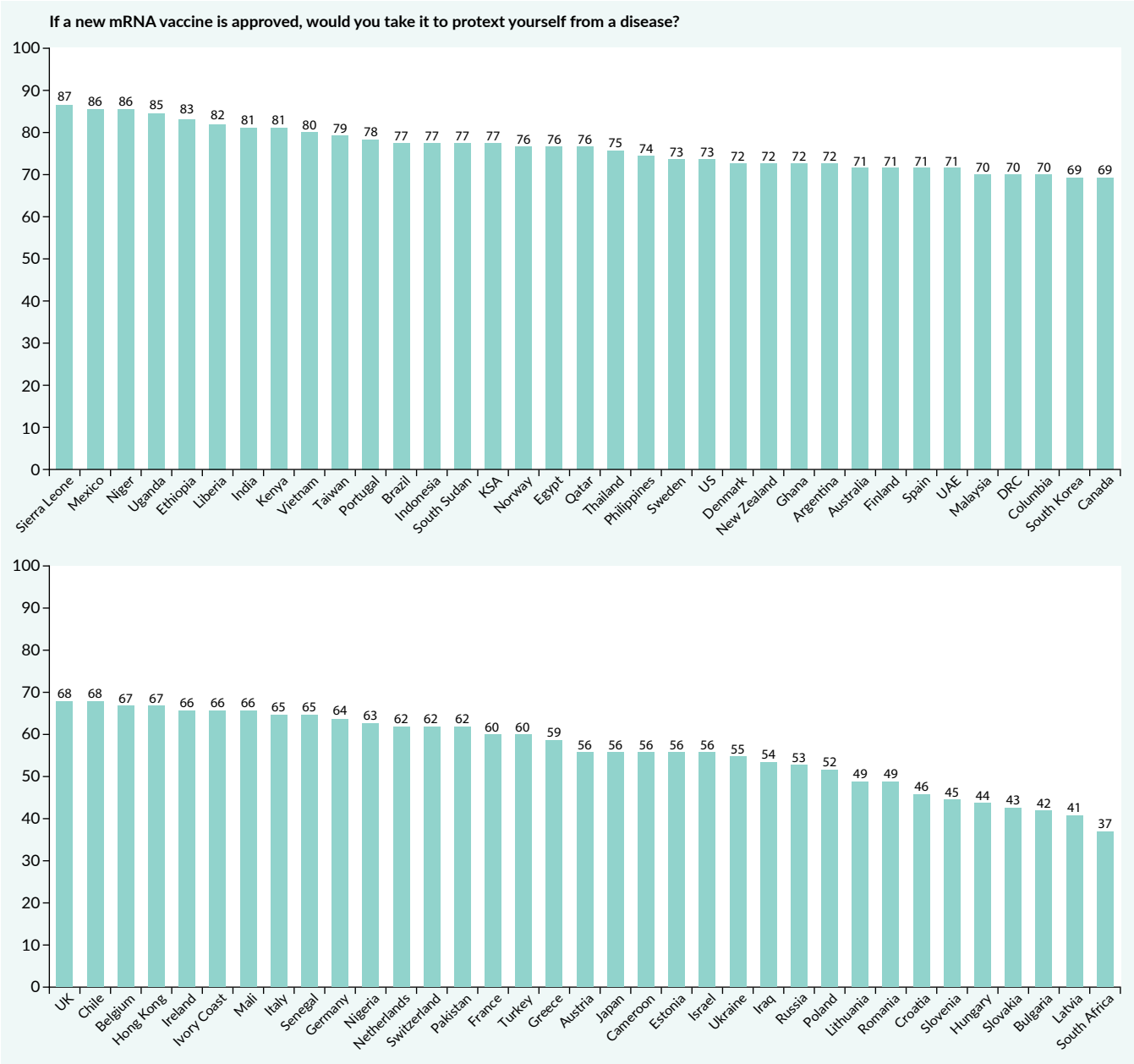
When we look at the willingness to accept another new mRNA vaccine if approved (Figure 1), the reported willingness was higher than the reported knowledge of mRNA. Seventy-three percent of the US respondents were willing to take a new mRNA vaccine, while 66% of Côte d'Ivoirians, 81% of Kenyans, 72% of Ghanians, and 63% of Nigerians reported willingness to accept a new mRNA vaccine, despite the lower levels of awareness about mRNA.

This seeming discrepancy should be seen as an opportunity. There is willingness, but there is inadequate information and understanding. If the scientific and public health community does not act to address this gap before we have new mRNA vaccines or therapeutics available, we may lose those who are willing to accept these products because they turn to social media or become vulnerable to misinformation in the absence of accessible, clear, and relevant information about mRNA. As Atwell and colleagues state in their important study, 'Government systems that leave some populations behind increase those populations' susceptibility to misinformation' [5].

We need to use the time we have before the launch of new mRNA vaccines and therapeutics to build trust and confidence now. To do that we need to listen and understand the concerns and questions as well as the realities of the people we aim to reach. That calls for a closer collaboration between scientists working on mRNA vaccine and therapeutic opportunities—including social scientists—and relevant public health and policy partners.

FIGURE 1

Global Listening Project survey results on willingness to take a new mRNA vaccine, by country.



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Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has received research grants from Merck and J&J for the Vaccine Confidence Project.

Funding declaration: The author received financial support from GSK, Moderna and the MacArthur Foundation to the Global Listening Project for the research referenced in this article. No funding was provided for authorship and/or publication.

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Article source: Invited.

Revised manuscript received: May 14, 2024; **Publication date:** May 21, 2024.

MAY 2024
Volume 3, Issue 3

VACCINE INSIGHTS

LATEST ARTICLES

INTERVIEW

Is there a role for vaccines in combatting the opioid epidemic?

Fentanyl is at the center of the opioid crisis in the USA, causing an increasing number of overdoses and deaths. **Casey Nevins**, Assistant Editor, *Vaccine Insights*, speaks with **Elizabeth Norton**, Associate Professor, Tulane School of Medicine, about her work in developing a mucosal vaccination tailored to protect the brain from the effects of fentanyl.

Vaccine Insights 2024; 3(3), 83–89

DOI: 10.18609/vac.2024.017

Q What influenced you to start working with vaccines?

EN: Like many budding scientists of my generation, I grew up reading *The Hot Zone* by Richard Preston (a bestselling nonfiction book about viral hemorrhagic fevers) and became interested in infectious disease research. I studied at Emory University for my undergraduate degree and while there, I was fortunate enough to work at the Centers for Disease Control (CDC) in Atlanta, Georgia, researching sepsis in children from Africa. I loved that experience of asking questions and being in the lab to obtain answers. This led me to continue my education and post-doctoral fellowship at Tulane University. There, I investigated mucosal

vaccination under the mentorship of John Clements PhD, the former Chair of the Department of Microbiology and Immunology. Since then, I have carried out research on mucosal vaccination as an independent investigator at Tulane.

Q What immunotherapeutic advantages does a vaccine targeting fentanyl offer in mitigating the physiological and behavioral effects associated with its abuse?

EN: For fentanyl substance abusers, the vaccine would stop the effects of the drugs by blocking the molecule from getting into the brain and binding to the body's opioid receptors. This would prevent the effects of fentanyl including respiratory suppression, which in its most severe form results in acute respiratory failure leading to overdose and death. The vaccine would also eliminate the high that comes with taking opioids, which makes the drug less attractive to users. Also, because the vaccine specifically works on fentanyl, it does not stop the effects of other drugs used for pain management. For example, someone could still effectively use morphine after being vaccinated.

By blocking the effects of the drug, you can block a potential reinstatement of craving after an abuser comes off fentanyl with other therapy programs. For individuals with substance abuse, the vaccine is designed to work in parallel with other therapies in order to prevent relapse, overdose, and death.

Other populations protected by a vaccine would be the unintended victims of fentanyl. Fetanyl effects are so potent that material much smaller than the size of a coin (~2 mg) can be lethal. Unintential use includes people taking a powder or pill drug obtained outside of a pharmacy without knowing that it has been laced with fentanyl. Emergency responders like police or military personnel can also come into accidental contact with illicit fentanyl or fentanyl-laced drugs during their routine job duties. A vaccine for this population would also prevent the fentanyl from having any toxic effects on the body.

Q What insights or challenges from prior fentanyl vaccine studies have influenced the design and methodology of your investigation [1]?

EN: Prior studies that have investigated vaccines for drugs of addiction have taught us that we can block the effects of the compound with antibodies to prevent drug intoxication, drug cravings, and re-addiction in the case of relapse. These antibodies can be generated by vaccination with a conjugate antigen, meaning the drug gets chemically attached to a carrier protein. The resulting antigen is immunogenic but lacks any of the original stimulatory ability of the drug when administered to the body.

"The right adjuvant and delivery route can mean the difference between protection and non-protection in mechanisms that are not always anticipated."

Previous studies have all focused on making high levels of antibodies after injected vaccination by adding adjuvants to the conjugate antigen. They reasoned that a vaccine that generates the highest titers of serum isotype immunoglobulin G (IgG) would bind to the compound, sequester it in the periphery, and keep it away from the brain.

For our study, we aimed to achieve high levels of antibodies in mice, but we also focused on comparing adjuvants and routes of delivery. The right adjuvant and delivery route can mean the difference between protection and non-protection in mechanisms that are not always anticipated.

Q Why did you choose the dmLT and LTA1 adjuvants?

EN: I have been working on versions of these adjuvants for about 20 years now. They are unique since they can be used mucosally as well as parenterally. They have been really interesting molecules to study and my and others' research into how they can be applied to different vaccines has led to many unexpected findings [2,3].

dmLT is a double mutant of the heat-labile enterotoxin or LT, and it is a safer but still effective form of the native LT protein. You can use it orally, sublingually, or by injection. About 10 years into my research, I decided to design a better form of dmLT that does not contain its binding subunit, so it could be used nasally. This new form is LTA1, which is composed of the A1 enzymatic active domain of dmLT and its parent molecule, LT. However, unlike dmLT and LT, LTA1 does not bind to GM1 ganglioside on neuronal tissue and has no evidence of causing cranial nerve damage.

dmLT has successfully been tested in a series of clinical trials alongside a number of antigens, including for enterotoxigenic *Escherichia coli* and polio virus. LTA1 has not yet been tested in a clinical trial, but we are using it to develop a *Klebsiella pneumonia* vaccine, in collaboration with Jay Kolls here at Tulane University, which is scheduled for a first-in-human study in 1–2 years.

One thing that we were interested in when we first started our fentanyl study is the fact that a lot of opioid-use therapies involve buprenorphine films that are taken buccally or sublingually. There are also potential mucosal drug exposures including powder inhalations. We thought it would be highly relevant for this patient population if we could develop a mucosal approach that could be combined with the delivery of buprenorphine to help control and manage cravings, and a periodic mucosal vaccine dose to maintain high levels of antibodies.

Q What did you find regarding the effectiveness of different adjuvants and delivery routes?

EN: As I said, similar to previous studies, we wanted both high levels of antibodies and to show that we are blocking the effect of the drugs. However, because we were testing dmLT and LTA1, which can be given orally, sublingually, or intranasally, we also wanted to explore different routes.

In our study, we compared the effects of the gold standard adjuvant for achieving high levels of antibodies (intramuscular alum) to intramuscular dmLT, sublingual dmLT, and intranasal LTA1. The mucosal routes all started as an intramuscular prime with subsequent mucosal boosters, since we reasoned that the prime vaccination would cause a high level of systemic IgG and the mucosal boosters would work to maintain that response over time.

Interestingly, we identified high levels of anti-fentanyl antibodies in all of our vaccine test groups. However, when it came to blocking the drug from entering the brain, the best levels of protection from vaccination were observed with the mucosal booster groups—sublingual dmLT or intranasal LTA1. However, dmLT given parenterally can also protect animals from fentanyl [4].

Q What surprised you about your results?

EN: We were curious why the mucosal groups showed a better immune response, since all the groups had high levels of antibodies of the main serum isotype IgG to fentanyl. An older study had observed that protection from opioids (e.g., oxycodone) and antibody isotypes generated in response to vaccination could be manipulated immunologically during immunization, much like altered adjuvant danger signals to the immune response [5]. Thus, we investigated further, looking for antibody affinity and antibody isotypes IgG1, IgG2, and IgA. To our surprise, the best correlation of protection was found in animals with the highest levels of IgA against fentanyl. This is surprising since IgA is expressed highly at mucosal surfaces whereas IgG is highest in circulating blood.

Upon some additional literature review, we discovered that gut-educated IgA plasma cells have been found to defend the meningeal venous sinuses [6]. Essentially, oral or mucosal exposure to pathogens induces plasma cells that travel to the brain. These tissue-resident plasma cells express high levels of antibodies so that when a mucosally-introduced antigen enters the bloodstream, it becomes trapped in the meninges and does not cross into the brain.

In our study, I think we may have tapped into this sophisticated mechanism for protecting the brain. I like to think of mucosal vaccination in the settings of substance abuse drugs as the means to create an antibody helmet. We are ensuring high levels of antibody around the brain, which is not necessarily reflective of the antibody levels in the bloodstream. However, further research is needed to confirm that this is indeed occurring with our vaccination approach.

"...in order to protect the brain from substance abuse drugs we need a vaccination approach that is more sophisticated than just a generation of the highest level of circulating IgG."

When we discovered the importance of IgA, with the help of my collaborators Tom Kosten at Baylor College of Medicine and Colin Haile at the University of Houston, we re-examined data from Tom Kosten's previous clinical trial on a vaccine to stop cocaine addiction [7]. Though his study ultimately did not achieve its clinical endpoints, there were a small number of people who had significantly less cocaine use after they were vaccinated. Upon further investigation, we observed that IgA and not IgG levels were correlated to people who stopped or reduced their use of cocaine after vaccination versus the people who had not [8].

I believe that in order to protect the brain from substance abuse drugs we need a vaccination approach that is more sophisticated than just a generation of the highest level of circulating IgG. Tissue-resident antibody-secreting cells and antibody isotypes are likely critically important.

Q What are the potential challenges in implementing a fentanyl vaccine on a larger scale?

EN: When you go from research to commercialization, one of the challenges is always manufacturing. You must manufacture large amounts of vaccine in a way that is not too costly. Another challenge is that fentanyl hapten is classified as a Schedule 1 drug, which affects how we can manufacture our vaccine. Manufacturers need a Schedule 1 license to work with fentanyl hapten and will have to implement careful safety procedures during conjugation reactions.

Another challenge has to do with delivery. There are still important questions that we must answer, likely during clinical trials, such as: will we end up using the injected form of the vaccine in humans? Will that mucosal booster be a critical step or can parenteral immunization with the right adjuvant also work? If mucosal delivery, will a delivery device also be necessary?

Furthermore, we must consider the duration of vaccine-mediated protection. This is an important point because of the practical concerns that come with multiple vaccinations, but also because some users may end up not wanting that protection. If you have someone who really wants to use fentanyl, will the vaccine block them permanently? Someone may intentionally try to use more fentanyl to overcome the vaccine's effects, could this put them at a higher risk of overdose and death if vaccine-mediated immunity decays overtime? We need to know the limits of the vaccine, and how those limits might affect its users.

Q How might your findings contribute to the broader understanding of immunotherapies for substance use disorders?

EN: If we are able to show that IgG or IgA tissue-resident antibody secretion is the most important target, it could radically change how vaccine studies are being designed. Right now, for any vaccine to treat drugs of addiction, researchers look to drive the highest level of serum IgG. If we appropriately change the narrative to the key mechanisms of protection (e.g., driving the highest level of meningeal plasma cells to protect the brain), then we could design better vaccines for anything related to protecting the brain.

Q Looking to the future, what are your key goals or priorities in terms of your research?

EN: It would be wonderful to be part of the team that gets a commercial product on the market to prevent fentanyl or other causes of death, pain, and suffering. Regardless, I am lucky to be able to participate and contribute to the knowledge that changes how vaccines are designed or how we approach what drives protective immunity.

We are all standing on the shoulders of giants, and I have so much appreciation for the scientists who have come before me. It would be great to add another block in the pyramid that is human knowledge and mentor the next generation of scientists along the way.

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BIOGRAPHY

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Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author is a consultant for OVAX, Inc. She is also a co-inventor on a fentanyl vaccine patent (adjuvanted conjugate opioid vaccine).

Funding declaration: The author has received NIH/NIAID grants.

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Article source: Invited.

Interview conducted: Jan 30, 2024; **Revised manuscript received:** Apr 22, 2024;

Publication date: May 9, 2024.

VACCINE INSIGHTS

ERRATUM

Erratum to: A fresh look at analytical methods for vaccines

Timothy Schofield

This erratum contains corrections to the article: Schofield T. A fresh look at analytical methods for vaccines. *Vaccine Insights* 2022; 1(5), 247–258.

In the version of this article initially published, there were several typographical errors. The correction is listed in full below. The corrections were made to the HTML and PDF versions of this article as of May 21, 2024; the amended article may be accessed here.

Vaccine Insights 2024; 3(3), 81–82

DOI: 10.18609/vac.2024.016

In the section SPECIFICATIONS & THEIR ROLE IN THE VACCINE ANALYTICAL METHOD LIFECYCLE (paragraph 2, pp 248–249), the original article read:

- A definition of satisfactory patient outcome (e.g., equal to 95% efficacy) is translated to a limit on a vaccine biomarker (correlate of protection);
- The correlate of protection is used in vaccine clinical studies to define a limit on a critical quality attribute (a specification limit);
- The specification limit is used to define limits on critical process parameters (a design space).

The corrected article reads:

- A definition of satisfactory patient outcome (e.g., p_{limit} equal to 95% efficacy) is translated to a limit on a vaccine biomarker (correlate of protection; z_{limit});

- The correlate of protection is used in vaccine clinical studies to define a limit on a critical quality attribute (a specification limit; y_{limit});

- The specification limit is used to define limits on critical process parameters (a design space; x_{limit}).

In the same section (paragraph 4, p. 249), the original article read:

Thus, limits in **Figure 1** (e.g., or Design Space) are derived from the appropriately budgeted portions of the specification range.

The corrected article reads:

Thus, limits in **Figure 1** (e.g., x_{limit} or design space) are derived from the appropriately budgeted portions of the specification range.

In the sub-section **Method control** (paragraph 2, p. 252), the original article read:

In this depiction the specification limit (or the analytical budget,) is used to define the ATP , where v and w represent performance parameters such as accuracy and precision. The relationship between a critical method parameter (u) and performance parameters can be used to derive a method parameter limit (, in red), while the relationship between a suitability parameter (s) and the performance parameters can be used to derive a system suitability limit (, in green).

The corrected article reads:

In this depiction the specification limit (or the analytical budget, y_{limit}) is used to define the ATP (v_{limit}, w_{limit}), where *v* and *w* represent performance parameters such as accuracy and precision. The relationship between a critical method parameter (*u*) and performance parameters can be used to derive a method parameter limit (u_{limit}, in red), while the relationship between a suitability parameter (*s*) and the performance parameters can be used to derive a system suitability limit (s_{limit}, in green).

In the same sub-section (paragraph 4, p. 252), the original article read:

System suitability parameters provide additional control. Like critical parameter parameters, these can be established through a model between performance characteristics...

The corrected article reads:

System suitability parameters provide additional control. Like critical method parameters, these can be established through a model between performance characteristics...

In the sub-section **Some statistical opportunities** (paragraph 2, p. 254), the original article read:

$U\_RV=t_{\alpha,n-1}) (\sigma/\sqrt{n})$. The factor is a statistical constant associated with a probability equal to α and with n−1 degrees of freedom.

The corrected article reads:

$U_{RV}=t_{\alpha,n-1}) (\sigma/\sqrt{n})$. The factor $t_{\alpha,n-1}$ is a statistical constant associated with a probability equal to α and with n−1 degrees of freedom.