WORKSHOP REPORT

Vaccines - Are regulatory and funding approaches fit for purpose for the next decade?

13-14th June 2024
Hyatt Regency Hotel, Tyson's Corner
Virginia, USA

CIRS Centre for Innovation in Regulatory Science

Section 1: Executive Summary

Background

Over the last four years there has been much greater attention paid by industry, regulators, health technology assessment (HTA) bodies and the general public to vaccines for a range of reasons. These include:

- The COVID-19 pandemic. Various estimates suggest that the rapid development and deployment of vaccines for COVID-19 saved over 20 million lives.
- Emergence of new vaccine technologies, in particular mRNA vaccines, which have enabled vaccines to be developed in months rather than over several years, increasing the pipeline and its attractiveness to industry and investors.
- A wide range of previously difficult to vaccinate against diseases now appear to be potentially preventable through vaccination.
- The importance of vaccination of adults against key diseases is increasingly recognised, and several new vaccines for adult use have recently been developed.
- After years of very limited success, a number of successful clinical trial results for several cancer vaccines have recently been reported.

With these changes to the landscape, new development, regulatory and funding paradigms are needed for vaccines. With the main exception of some therapeutic vaccines for infectious diseases and the cancer vaccines under development, unlike medicines, vaccines are typically administered to larger, healthy populations to prevent, rather than to treat, a disease. This affects the design of programmes for vaccine development and commercial risks in development, regulatory assessment of benefit, risk and uncertainty and HTA decisions affecting payment for vaccinations by insurers and governments.

Vaccine development and deployment can involve high commercial risk, although investments from government programmes such as the Biomedical Advanced R&D Authority (BARDA) in the US, from philanthropic organisations such as the Bill and Melinda Gates Foundation or global coalitions such as the Coalition for Epidemic Preparedness Innovations (CEPI), can reduce risk and strongly influence the vaccine development agenda. The payment models for vaccines need to evolve to reflect the level of commercial risk in vaccine development and the wider benefits to family, carers, community and the economy that come from vaccination. It is important to establish agreement between stakeholders on what measures of vaccine efficacy and cost-effectiveness will be considered adequate to enable regulatory approval, recommendations by National Immunisation Technical Advisory Groups (NITAGs) and funding by governments to support vaccine deployment.

In this workshop, CIRS brought together senior representatives from the international pharmaceutical industry, regulatory agencies, NITAGs, HTA agencies, payers and academia to identify challenges and opportunities to enable vaccine regulatory and funding approaches fit for the next decade.

Workshop objectives

This multi-stakeholder workshop consisted of a series of sessions (see programme) featuring presentations and panel discussions, as well as three parallel roundtable discussions. The objectives were to:

- Review and discuss the changing vaccine landscape and what the opportunities and challenges are within and across development, regulatory, HTA agencies and NITAGs.
- Identify critical information gaps and how regulatory and HTA/NITAG systems need to evolve to accommodate new vaccine technologies.
- Propose options and make recommendations on how to address policy challenges in the development, regulation, HTA and funding for vaccines.

Key points from presentations and open-floor discussions

Why vaccines and why now?

This was the first CIRS workshop held on vaccines, but it built on many years of CIRS experience in regulatory and HTA agency performance metrics, and research on new approaches to assessment of product benefit/risk and evaluating HTA and payer approaches. The answer to "why vaccines and why now" is more than just learning from the experience of COVID-19. There was already a renaissance of interest in vaccines prior to COVID-19 with respect to both technology and usage. Then COVID-19 brought forward strides in development and a whole series of new challenges. A resurgence of some vaccine hesitancy and discussions around adherence also occurred.

It is an interesting time to be discussing vaccines as there is now the potential to do three things:

- Develop vaccines for diseases that still don't have effective prevention strategies or can be difficult to treat, such as HIV and tuberculosis.
- Develop vaccines for existing diseases but with increased efficacy
- Increase the uptake of existing vaccines for diseases that are not well-managed.

Vaccines drive different kinds of discussions compared to other types of products, for example, discussions around collective benefit, public good, herd immunity etc. Vaccine equity is also a hotly debated topic. The COVID-19 pandemic highlighted the critical need for equity consideration in vaccine health policy.

Clear criteria and guidance on expectations from regulators are essential

The publication of the US Food and Drug Administration (FDA) guidance on what would be a successful COVID-19 vaccine was pivotal during the pandemic. Vaccine developers knew what kinds of trials for efficacy they had to design to meet regulators' expectations. There were also important discussions on the need for data in paediatric, pregnant, elderly, ethnically diverse and immunosuppressed patients, and criticism from some that this data should have come earlier. Prophylactic antibodies were viewed as medicines rather than vaccines with potential procurement implications.

To ensure good evidence-based public health recommendations, as soon as possible after regulatory approval, there needs to be information exchange between vaccine developers, regulators, HTA bodies and NITAGs. Structured processes for communication allow for sharing of data - not just clinical data, but economic, epidemiologic, and cost-effectiveness data.

In terms of the applicable regulatory framework and how vaccines are assessed, this is very dependent on the jurisdiction and the target indication. Having a structured approach and guidance from the regulator is critical to ensure that vaccine development is successful.

Vaccines are undervalued

There is a need to reflect on just how important vaccines are as one of the cornerstones of public health. Even with the existence of very effective vaccines against shingles and influenza, and the COVID-19 boosters, adult uptake is low. While people are not generally opposed to vaccines, there is a lot of apathy and hesitancy. The durability of response to a particular vaccine can be important in determining its value, but if a vaccine provides a lifetime or 5 or 10-year response, the discount rates that are currently used often undervalue that vaccine. In a recent Office of Health Economics (OHE) study across a sample of countries, the benefit-cost analysis of four immunisation programmes showed that adult vaccines can return up to 19 times their initial investment to society, by preventing and reducing morbidity and mortality, reducing health care costs, increasing productivity, social equity, and delivering other broader societal values. There is also a need to simplify vaccination schedules.

Clear and authoritative communication on vaccines must be prioritised

Ensuring that information sharing on vaccines comes from authoritative sources, and engaging communities that have issues with vaccine confidence and hesitancy, is important to address misinformation. Individual patient risk/benefit tolerance will vary significantly. People make vaccination decisions in the wider social world setting. Individuals who are

vaccine hesitant tend to seek a lot of information before deciding and are more at risk to encounter misinformation or disinformation. Indirect exposure to uncommon and rare adverse events can decrease the acceptance of vaccines. Indirect exposure to unproven false serious adverse events also decreases vaccine confidence, but having experienced a common adverse event does not impact someone's intention. Experts and the public perceive risks differently. While experts conduct evidence-based analysis, the public is often driven by emotion. What is the role of the regulator to communicate the benefit-risk of a vaccine?

Vaccine development needs de-risking

New therapeutic targets, technologies, approaches, adjuvants and delivery routes are all being explored. Today, developers are looking at close to a billion US dollars for every vaccine that is developed. In the early stages, a vaccine programme costs around $10 - $20 million, but as soon as the vaccine enters the clinic, this escalates exponentially. In part, this is due to the requirement by regulators and HTA bodies for much larger clinical trial populations to be used for the evaluation of many vaccines than for most medicines. Approximately 10% of the vaccine candidates in the clinic proceed to licensure and launch; this is an area that needs de-risking.

Speed has a couple of advantages; it is not just about reaching the market, but to reduce the cost. Succeeding or failing quicker allows developers to relocate resources to more promising programmes, diversify targets and work on multiple technologies.

Managing risk

Market risk is much more challenging when moving into new disease areas where the vaccine demand is unknown. Is it going to be restricted to a narrow population of individuals at increased risk, or is it going to be more routinely recommended, and deployed in populations where the demand could be much higher? Early engagement with key stakeholders involved in national immunisation programmes is vital to get a better assessment of the potential vaccine demand, as well as to understand the pathway to market access for these products.

No one would have believed at the beginning of the COVID-19 pandemic that there would be multiple vaccines coming through and administered to the public within 12 months. That was only possible because research and commercial stakeholders were ready to take commercial risks (such as manufacture in advance of regulatory approval), and regulators were ready to adapt the regulatory systems. Every stakeholder involved in vaccine development is now considering the learnings from that experience.

When considering the concept of risk, there needs to be thought given to what risk, whose risk, and who bears that risk, including the risk to societies and healthcare systems of not taking the challenge on. In addition, what's the level of risk tolerance? Who defines it? Who is accountable to whom? What is known and unknown? During the COVID-19 pandemic, uncertainty and risk had to be accepted, and there was a big benefit in doing that.

New regulatory and funding approaches for vaccines are needed

Use of surrogate endpoints (such as correlates of protection) which are reasonably likely to predict the clinical benefit, in combination with managing uncertainty through post-approval effectiveness studies, are part of new approaches to vaccine regulation, coverage and funding decisions. The value of vaccination to the broader healthcare system and economy will need to be considered in future funding models.

In many parts of the world, regulations do not include extraordinary procedures for regulation of a pandemic vaccine, so during the COVID-19 pandemic, many regulators demonstrated flexibility in existing regulatory procedures. Developers and regulators are now exploring the use of platform approaches for vaccines, which can be quickly updated to the strain that is causing a pandemic, or more broadly enable the use of existing knowledge about related products to simplify development and regulatory review of a related vaccine.

All stakeholders recognise that the COVID-19 pandemic was an extreme, urgent situation, and some of the approaches employed during the pandemic may not be sustainable in the long run. However, it is also recognised that it would be a missed opportunity not to further leverage particular efficiencies gained, such as additional opportunities for early engagement and use of reliance, not only for future pandemic regulatory situations, but also for routine regulatory review of vaccines and other medical products.

The use of reliance pathways, including for vaccines, is gaining momentum. There are a range of different reliance practices, starting with basic collaboration and information sharing, building up to reliance and work sharing, and ultimately to full recognition. The benefits of using these approaches include not only more timely access to safe and effective and quality products, but more efficient use allocation of resources, both on the industry side and on the regulatory authority side. It is important to recognise that there are also barriers to reliance practices. One of those is demonstrating the sameness of a product across different regions, even if it comes from the same production line or is the same commercial product manufactured on different production lines. In addition, making sure that there's clarity on the requirements for access to regulator-generated documentation and the documentation that was submitted to the reference authority.

Regulators like the European Medicines Agency (EMA) and US FDA offer important opportunities for vaccine developers to engage with them early in development to discuss study designs and expectations for evidence generation. There are also more limited opportunities in some regions to engage with HTA agencies, however NITAGs are less commonly involved directly and regularly with vaccine developers. The NITAG plays a critical role for recommending the vaccine, therefore it is essential to continue to work together and find adequate forums to exchange information early enough, with all relevant stakeholders, on their respective perspectives.

Recommendations from roundtable discussions

What collaborative evaluation models and metrics should be developed to support vaccine regulatory or funded access?

- Horizon scan of the definition of “vaccine”, including how the term is communicated in society. Without a common lexicon, it's hard to have further discussions on what metrics could be utilised. A definition that can be future-proofed is needed, but this should not be so prescriptive that any new future technology is excluded.
- Horizon scan of vaccine regulatory, HTA and NITAG frameworks. Why, outside the COVID-19 pandemic, is it often taking longer to evaluate vaccines versus other products?
- Evaluate reliance use and challenges, following horizon scanning on the landscape of vaccine definition and applicable regulatory, HTA and NITAG frameworks. An understanding is also needed of the specific issues impacting how to apply reliance processes to vaccines as opposed to other drug products.
- Bring stakeholders together to discuss the business case for a company to continue manufacturing a vaccine when patients are not receiving it.

How do we evolve the regulatory system to accommodate new vaccine technologies and challenges?

- Harmonised definition of preventive vaccine vs therapeutic vaccine is needed.
- Reflect on the size of safety database needed for therapeutic vaccines compared to preventative vaccines.
- Need greater clarity on use of human challenge studies, not only for understanding the risks, but also for use as pivotal data for a given product.
- Need platform guidance coherent across jurisdictions, starting with CMC and toxicology. Expand in a stepwise approach to clinical safety, change control management for lifecycle management and post-approval changes. Not all countries are at the same stage of acceptance for platform technology, and this may create delays in access.
- Expand use of real-world evidence (RWE) for vaccines. Leverage the RWE process that Brazil has put in place as a good example for other countries and in support of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) concept paper in development.

How can we ensure that vaccine health economic assessment/HTA is fit for the future?

- Ensure there is a formal deliberate and iterative process for information exchange between manufacturers, NITAGs, and HTA bodies, including the patient perspective. Early engagement is key to allow inclusions of endpoints in the clinical development plan for phase 3, but also allowing an iterative process as the data matures.
- Support increased NITAG capacity and investment in talent / skills for NITAG reviewers. The independence of the agency must be maintained, with management of potential for perception of conflict of interest.
- Petition governments for greater funding in terms of NITAG resource, and talent retention.

INFOGRAPHIC SUMMARY

CIRS brought together pharmaceutical companies, regulatory agencies, National Immunisation Technical Advisory Groups (NITAGs), HTA agencies, payers and academia to make **recommendations** on how to address **policy challenges** in the development, regulation, HTA and funding of **vaccines**.

Vaccines are under valued

Key recommendations:

- **International collaboration on evidence generation**
- **Evolution of regulatory, HTA and NITAG frameworks**
- **Common lexicon of definitions**
- **Clear and consistent communication of value to society**

Increased vaccine confidence and uptake

Workshop programme

Please note, affiliations are stated as they were at the time of the meeting.

Day 1: 13th June 2024

SESSION 1: THE CHANGING VACCINE LANDSCAPE	
09:00	**Chair's welcome and introduction** **Dr Supriya Sharma,** Chief Medical Adviser, Health Canada
09:10	**Plenary presentation** **Vaccines: development, regulatory and funding challenges** What worked well for vaccine development and regulatory review during the COVID-19 pandemic? What challenges remain? **Dr Emily Erbelding**, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), USA
09:30	**New vaccine targets and technologies – what particular challenges and solutions exist?** • New targets – difficult to vaccinate infectious diseases, emerging infectious diseases • Approaches to cancer vaccines • Newer vaccine technologies – mRNA, DNA vaccines, viral vectors, recombinant fusion proteins, new adjuvants • What are the technical, regulatory and funding implications for the blurring definition between vaccines and therapeutics? **Prof John Skerritt,** Enterprise Professor for Health Research Impact, University of Melbourne, Australia
09:50	**Discussion**
10:00	**Vaccines for adults** This plenary and panel discussion addressed the following questions: • What are the vaccine development opportunities? • How is benefit and risk best evaluated by regulators for vaccines for low frequency, high consequence infectious disease? • What regulatory approaches are most applicable to oncology vaccines? • What funding models are appropriate? When is the private market viable? How will therapeutic vaccines be resourced and what role does public preference play in the funding? • How can vaccine uptake be improved? What can government and industry do to raise healthcare professional and public awareness? How can agencies be supported in overcoming misinformation? **Dr Peter Marks,** Director, Center for Biologics Evaluation and Research (CBER), FDA, USA
10:20	**Panel Discussion – 5 minutes' viewpoint from each panellist followed by discussion / Q & A** **Dr Peter Marks,** Director, Center for Biologics Evaluation and Research (CBER), FDA, USA **Dr Shelley Deeks**, Deputy Chief Medical Officer, Nova Scotia Department of Health and Wellness, Canada **Dr Gowri Raman,** Associate Director, New Technology Engagement, Patient-Centered Outcomes Research Institute (PCORI), USA **Richard Hughes IV**, Partner, Epstein Becker & Green PC, USA
11:00	**Break**

SESSION 2: DE-RISKING VACCINE DEVELOPMENT

This plenary and panel discussion addressed the following questions:

- What approaches can companies use to de-risk technical aspects of vaccine development?
- Are there some tips for successful clinical trial design?
- How can clarity on regulatory and payer expectations be achieved?
- What incentives can be deployed to stimulate development of vaccines for low incidence diseases?
- It is possible to be able to better predict anticipated vaccine demand, especially for adult vaccines?

11:30	**Plenary presentation** **Kumaran Vadivelu,** Head, Vaccines Development, GlaxoSmithKline, USA
11:50	**Panel Discussion - 5 minutes' viewpoint from each panellist followed by discussion/ Q&A** **Kumaran Vadivelu,** Head, Vaccines Development, GlaxoSmithKline, USA **Sophie Sommerer,** Director General, Biologics and Radiopharmaceuticals Drugs Directorate (BRDD), Health Canada **Dr Robert Johnson,** Director, Medical Countermeasures Program, Biomedical Advanced R&D Authority (BARDA), USA **Phyllis Arthur,** EVP & Head, Healthcare Policy and Programs, Biotechnology Innovation Organization (BIO), USA
12:30	**Lunch**

SESSION 3: REGULATORY CHALLENGES AND METRICS

This session addressed the following questions:

- Challenges with clinical trials – size and coverage; How much vaccine efficacy is required? Can impacts on disease transmission/progression be reliably demonstrated?
- Platform approaches in vaccine development and regulation – can development and review of vaccines be streamlined?
- Precision versus mass vaccination – implications with respect to the current regulatory (and funding) paradigms
- Can potential safety issues post licensure be better anticipated during vaccine development?
- Is greater regulatory cooperation and reliance possible?
- Are there other lessons from COVID-19?
- How will therapeutic vaccines be evaluated in the future both from regulatory and access perspective, as there does not seem to be a clear pathway currently in most major jurisdictions around the world?

13:30	**Chair's Introduction** **Prof Hans-Georg Eichler,** Consulting Physician of the Association of Austrian Social Insurance Institutions
13:35	**Regulatory considerations – perspective from ANVISA** **Dr Fabrício Carneiro de Oliveira,** General Manager (Head Office) of Biological and ATMP, ANVISA, Brazil
13:55	**Discussion**

14.00	**Plenary presentations - Vaccine safety and risk communication – meeting regulator, healthcare professional and community expectations (two 15 min plenary presentations)** **Vaccine safety – Dr Rita Helfand,** Senior Advisor for Science, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), USA **Vaccine risk communication to the public - Prof Eve Dubé,** Professor, Department of Anthropology at Laval University, Canada
14:30	**Discussion**
14:40	**What are the advantages of and potential barriers to regional alignment of regulatory review models for vaccines? (Two 15 min plenary presentations)** **Company view** – **Andrew Emmett,** FDA Liaison / Executive Director for US Regulatory Policy & Global Intelligence Pfizer, USA **Regulator view** – **Dr Claus Bolte,** Chief Medical Officer, Swissmedic
15:10	**Discussion**
15:20	**Break**

SESSION 4: ARE CURRENT HEALTH TECHNOLOGY AND NITAG ASSESSMENT MODELS FOR VACCINES FIT FOR PURPOSE?

This plenary and panel discussion addressed the following questions:

- What values could or should be included in HTA/NITAG assessments?
- How can these values be measured in an economically robust way? What are the data sources?
- Is there a role for assessment of equity issues – susceptibility, exposure and severity of the disease in disadvantaged populations?
- What types of comparators could be used, particularly when the vaccine is the first in class?
- Are there better models for when disease protection from vaccination accrues over many years/ lifetime or when vaccines treat very serious but rare infections?

15:50	**Plenary presentation – economic research group** **Prof Lotte Steuten,** Deputy Chief Executive, Office of Health Economics (OHE), UK
16.10	**Panel Discussion - 5 minutes' viewpoint from each panellist followed by discussion / Q&A** **Research group viewpoint – Peter Neumann,** Centre for Evaluation of Value and Risk in Health, Institute of Clinical Research and Health Policy Studies, Tufts University, USA **Company viewpoint - Craig Roberts,** VP, Outcomes Research, Merck, USA **Viewpoint from US ACIP - Dr Melinda Wharton,** Executive Secretary, Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC), USA **Viewpoint from European NITAG – Dr Jaime Pérez-Martín**, Head Prevention Service, Murcia Health Department, Spain
17:10	**Introduction to Syndicate Discussions**
17:15	**End Day one**
19:00	**Drinks Reception**
19:30	**Workshop Dinner**

Day 2 - 14 June 2024

SESSION 5: ROUNDTABLE DISCUSSIONS: PRIORITY RESEARCH AREAS AND HOW TO ADDRESS POLICY CHALLENGES	
08:00	**Syndicate A: What collaborative evaluation models and metrics should be developed to support vaccine regulatory or funded access?** **Chair: Prof John Lim,** Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Senior Advisor, Ministry of Health, Singapore **Rapporteur: Saiza Elayda,** Associate Director, Global Regulatory Policy, Merck, USA **Metrics -** There is currently very little vaccine-specific information on regulatory and HTA timelines/ approvals for vaccines compared with medicines. The existing CIRS metrics programmes could be extended. But what should it cover? **Collaborative evaluation models -** Is there a need for more structured mechanisms for collaborative evaluation of vaccines between regulators? Many emerging market regulators will struggle to have the technical capacity for reviewing new platform technologies – how can major regulators, industry, international foundations and CIRS support this?
	Syndicate B: How do we evolve the regulatory system to accommodate new vaccine technologies and challenges? **Chair: Dr Supriya Sharma,** Chief Medical Adviser, Health Canada **Rapporteur: Silvia Aiolli,** GRA Therapeutic Area Head mRNA Vaccines, Sanofi, Italy • Should therapeutic vaccines, including cancer, be regulated as drugs or vaccines? How could individualised vaccine therapies be regulated when every patient will receive a unique product? • What information on the types of evidence is required by regulators? e.g. clinical trials, natural vs challenge trials, immunological correlates • What is needed to develop and better align regulatory approaches for new vaccine platform technologies (e.g. mRNA and viral vector vaccines)? • Are approaches for the use of real world evidence in supporting vaccine label extensions to different populations clear enough? • What role do regulators have in communicating benefits risks and safety issues with vaccines?
	Syndicate C: How can we ensure that vaccine health economic assessment/HTA is fit for the future? **Chair: Prof Hans-Georg Eichler,** Consulting Physician, Association of Austrian Social Insurance Institutions **Rapporteur: Joseph Kelly**, VP, Global Pricing and Market Access Head, Vaccines, GlaxoSmithKline, USA • How can the value that vaccines provide be better assessed? • Value assessment of vaccines - what approaches to include? Which outcomes other than direct health benefits should be explored to support funding decisions? • Is there a need for greater alignment of the evidentiary data required by regulators and payers? • What information should be made publicly available on the rationale for funding and coverage decisions? • What role should the patient voice have in vaccine funding and coverage decisions? • How can novel benefits like financial risk protection, peace of mind, societal health gains, healthcare systems security, political stability, social equity and macroeconomic gains, be included?

10:30	**Break, delegates to check out and synthesis of panel outcomes**
11:15	**Chair's Introduction - Prof John Skerritt,** Enterprise Professor for Health Research Impact, University of Melbourne, Australia
11:20	**Feedback by roundtable rapporteurs and discussion**
12:15	**Lunch**
SESSION 6: FUTURE VACCINE TECHNOLOGIES AND DEPLOYMENT	
13:00	**Chair's introduction - Dr Claus Bolte,** Chief Medical Officer, Swissmedic
	This plenary and panel discussion addressed the following questions: • What could the future vaccines development, regulatory and HTA ecosystem look like? • How are new vaccine technologies e.g. mRNA platform technologies being used in areas beyond infectious disease, such as therapeutic vaccines for oncology and rare diseases? • Is there a greater role for early scientific advice from regulators and HTA/NITAGs to increase the risk of development and reimbursement success? • Are special regulatory and funding pathways needed for vaccines that address unmet need and/or low prevalence serious diseases? • Do we manage uncertainty? Could managed entry or coverage with evidence development models be applied to vaccines? • What could greater data sharing and joint evaluation between HTA and regulators contribute? • Is the added therapeutic value of improved vaccine technologies or impacts on antimicrobial resistance adequately rewarded? • How can we put more onus on governments to cover vaccination schedules?
13:00	**Future vaccine development – Non-RNA perspective– Pascale Vintézou,** Vice President, Vaccines GBU Head, Sanofi, France
13:15	**Future vaccine development – mRNA perspective– Dr Charbel Haber,** Moderna, USA
13:30	**Panel Discussion - 5 minutes' viewpoint from each panellist followed by discussion/ Q&A** **Speakers Plus** **Academic viewpoint – Prof Lotte Steuten,** Deputy Chief Executive, Office of Health Economics (OHE), UK **Academic viewpoint - Richard Hughes IV,** Partner, Epstein Becker & Green PC, USA **Payer perspective – Dr Matthew Daley,** Senior Investigator**,** Kaiser Permanente Colorado, USA **BIO viewpoint: Phyllis Arthur,** EVP & Head, Healthcare Policy and Programs, Biotechnology Innovation Organization (BIO), USA
14:25	**Closing remarks**
14:30	**End of Workshop**

Section 2: Presentations

Please note that the following presentation summaries represent the views of the individual presenters and do not necessarily represent the position of the organisation they are affiliated with.

The slides featured in each of the following summaries is attributed to the individual presenter and has been reproduced with their permission.

Affiliations are stated as they were at the time of the meeting.

Session 1: The changing vaccine landscape

Vaccines: Development, regulatory and funding challenges

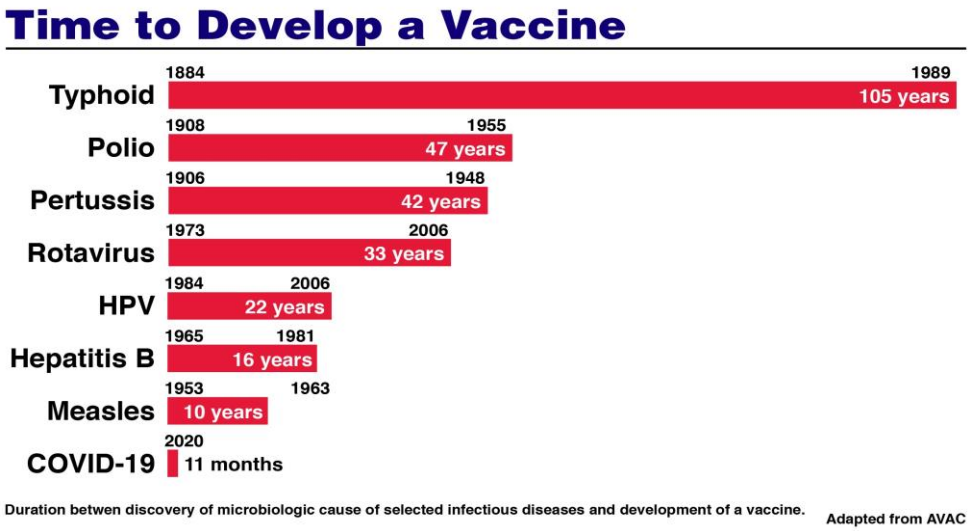
Dr Emily Erbelding, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), USA

The speaker's perspective was informed by participation in Operation Warp Speed, the US government's effort to develop vaccines, therapeutics and diagnostics and to roll them out during the COVID-19 pandemic.

What worked well?

COVID-19 vaccines were developed at an unprecedented pace (see slide below). The publication of FDA guidance on what would be a successful vaccine was pivotal. Vaccine developers knew what kinds of trials for efficacy they had to design to meet a regulator's expectations. Once the FDA published its guidance, it became clear that 30% efficacy for a vaccine was not going to be good enough to use it for COVID-19.

FDA worked very hard to keep up with the rolling submissions of the Investigational New Drug Applications (INDs) for COVID-19 vaccine developers. The phase one, two and three trials were all conducted in parallel, so as soon as data was available and judged to be sufficient, the vaccine developers were able to move quickly into the next phase.



The US government effort to accelerate clinical development of vaccines, therapeutics, and diagnostics for COVID-19 worked well, for example, the relationships and complicated reporting matrix that was created, bringing expertise from the Department of Defense, the Biomedical Advanced Research and Development Authority (BARDA) and National Institutes of Health (NIH) together.

The full capability of existing clinical trial networks was tapped into. A lot of their work was halted when the first lockdown happened and so they were available and very motivated to do something about the COVID-19 pandemic. Several clinical research organisation sites were pulled in.

Decisions were made quickly, such as the US government's decision not to use the platform trial design with a common placebo arm, even though early predictions had thought this would be very efficient. It was also discussed whether the US government should be the trial sponsor for all COVID-19 products, but it did not have the capability or capacity to do that, so this did not happen. It was a herculean effort for each company to bring their product to authorisation.

The Operation Warp Speed effort supported harmonised protocols. Rather than standardised protocols or a platform trial design, there were harmonised assays, allowing for a successful effort in assessing for correlates of protection across different platforms. There was also a single data and safety monitoring board put in place by NIAID for the efficacy trials.

The Advisory Committee on Immunization Practices (ACIP) recommendation that pregnant and lactating women should not be excluded from receiving authorised vaccines from the start, even though there was not much data to support safety in use, was a risk benefit decision. The obstetrician gynaecologists advocated for this strongly since there was no reason not to. There was no bad safety signal that emerged from the efficacy trials, even though there was not full data on safety in pregnancy because there was not enough time to have that data accumulated.

What were the challenges?

There were important discussions on the need for data in paediatric, pregnant, elderly, ethnically diverse and immunosuppressed patients, and criticism from some that this data should have come earlier.

Paediatric trials began soon after authorisation for adults, however some would say this was not soon enough. Investigators funded by NIAID published in September 2020 *Warp Speed for Coronavirus Disease 2019 (COVID-19) Vaccines: Why Are Children Stuck in Neutral?*, which was a criticism of the fact that paediatric trials had not already started. When this article went to print, developers were still in the middle of the efficacy trials for adults.

Could clinical data on people who are experiencing immunosuppression have been available earlier? This is an area where special populations perhaps did not get served well. There is a lot of heterogeneity in that group.

Another issue during the pandemic was that authorised vaccine doses that had been purchased by the US government were not available to researchers without company approval, as companies were still waiting for full FDA approval.

The term 'Operation Warp Speed' and how fast the operation moved may have contributed to vaccine hesitancy later. Although this is not a regulatory issue, there were certainly a lot of people that thought that the FDA moved too fast for the vaccines to be safe.

Future preparations

Resources were essentially unlimited during Operation Warp Speed. The US is now preparing for future threats with regular appropriations to ensure stakeholders could react quickly if needed. The US government interagency relationships are still intact.

Summary

- Clear regulatory guidance and rolling IND submissions facilitated rapid COVID-19 vaccine authorisation.
- Paediatric vaccine authorisation could have been accelerated.
- Vaccine safety data in pregnancy will always require time.
- Rapid effectiveness data for the immunocompromised will require innovative approaches.
- Additional resources (regulatory effort, advanced development, clinical trials) are needed for sustained response to emerging threats.

Vaccine targets and technologies – what particular challenges and solutions exist?

Prof John Skerritt, Enterprise Professor for Health Research Impact, University of Melbourne, Australia

There was already a renaissance of interest in vaccines prior to COVID-19 with respect to both the technology and new populations for their use. Then COVID-19 brought forward strides in development and a whole series of new challenges. It reignited interest in vaccines for regulators, research organisations and the wider health system. But vaccines are still underappreciated. Even though they are one of the cornerstones of public health, there are still only vaccines for 34 pathogens approved across the world, despite many more pathogens leading to serious disease.

Challenges

Funding for vaccine development, especially from a private venture capital market, is much less than for drugs. Government and philanthropy support fills the gap to some extent, however, government HTA bodies and payers are also under-investing in vaccines compared with medicines, despite the massive impact of vaccines and vaccination on public health over the last century.

Another challenge is low public uptake of many vaccines. Many countries report low vaccination rates among adults for shingles and influenza, as well as the COVID-19 boosters, for example. Too many children also miss their measles vaccines and as a result, there has been recent resurgence of the disease, even in developed countries. While only some people are overtly opposed to vaccines, there is a lot of apathy and hesitancy.

Vaccines traditionally have long development times and require large clinical trials which involve lengthy monitoring of the duration of protection. The bar for vaccine approval is quite high and appropriately so. Vaccines are usually administered to healthy populations (including children), so tolerance of adverse events is lower than for medicines. Rare but serious adverse events can be very hard to detect in clinical trials and attribution can be difficult.

The durability of response can be important in determining value, but if a vaccine provides a lifetime or 5 or 10-year response, HTA discount rates often undervalue that vaccine and the protection it gives over that longer period. There is also a need to simplify vaccination schedules, particularly if we are to encourage greater uptake of adult vaccination.

New approaches to vaccine development

Quite radical new approaches are being taken for use of vaccine technology, including in areas wider than infectious disease including certain cancers and rare diseases. Advances also allow better selection of antigens and use of new delivery routes, including patches and inhaled or oral vaccines. Patch vaccines are more stable at room temperature and intradermal vaccines can provide a much stronger response, with a lower dose than when used intramuscularly.

There has been a greater focus on bacterial vaccines in recent years, partly due to the importance of antimicrobial resistance. In addition, work is ongoing to develop a universal influenza vaccine. Increased durability of protection and the ability to block transmission are key targets for development of most vaccines for respiratory viruses. Increased vaccine thermostability is also important, especially for use in lower and middle-income countries. A specialised logistic system was needed for the very low-temperature storage and shipping of COVID-19 mRNA vaccines, although more recently a number of refrigerator-stable mRNA vaccines have been developed.

Definitions

There is a blurring between vaccines and therapeutics with a spectrum of products:

- Active immunisation (prophylactic vaccines) for infectious diseases, administered to healthy people.
- Therapeutic vaccines for infected people.
- Passive immunisation (MAbs) against infectious diseases.
- Cancer vaccines, including individual neoantigen and other therapies.
- mRNA and viral vector therapeutics - replacement of proteins using very similar technology to vaccines.

This means that aspects of both vaccine and drug regulatory/HTA approaches need to be considered with many of these products. International collaboration can be hindered because of a difference in definitions and regulatory pathways for vaccines in different jurisdictions. Batch release requirements (or lot testing) for vaccines are also different between regions.

Looking forward

The threat of the next epidemic or pandemic never really goes away. There is a need to be nimble in how vaccines are developed and regulated. Regulatory and HTA systems need to evolve, and vaccines must be valued more appropriately. Working together right across the public health spectrum will be critical in increasing vaccination rates.

Conclusions

- **Vaccine technology** is going through a (very) exciting phase – new targets, new technologies for development and delivery
- Need more **nimble development and regulatory approaches** – platform technology is critical
- **Regulatory and HTA systems must evolve** to the realities of vaccines in the 2020s
- **Vaccines are undervalued** – not just by payers but also by health systems and the public
- **Increasing vaccination rates** is critical for public health – concerning trends
- It is "when" not "if" for **the next pandemic** – we must be ready !

Vaccines for adults

Dr Peter Marks, Director, Center for Biologics Evaluation and Research, FDA, USA

Investment in vaccination has achieved significant public health impact including the near elimination of measles, rubella and polio and a reduction in human papillomavirus (HPV) infection rates in young women. Impact on vaccine-preventable illnesses in adults such as influenza, pneumococcal disease and respiratory syncytial virus (RSV) is important, while pertussis and shingles vaccination in particular populations is highly valuable (e.g. pregnancy, comorbidities and older adults). Yet vaccine uptake, including of COVID-19 vaccine boosters, is inadequate, even for the most vulnerable populations.

In a number of countries, adult vaccines are first introduced as self-pay (private funding) prior to government coverage. The government coverage process can take years and there can be significant morbidity/mortality over that time. How can this dynamic be changed to ensure that governments understand the value of vaccination to society?

The role of vaccines

There continue to be various emerging or reemerging infections, many of which are potentially vaccine preventable. It is a matter of how fast we can respond and what is worth going after. Key questions that need addressing include:

- How is benefit and risk best evaluated by regulators vaccines for low frequency, high consequence infectious disease?
- How can vaccine uptake/coverage be improved?
- What can government and industry do to raise healthcare professional and public awareness?
- What funding models are appropriate?
- How will therapeutic vaccines be resourced and what role does public preference play in the funding?

The regulatory framework

The benefit risk evaluation must consider if the potential side effects of a medicinal product are worse than the disease itself. The FDA benefit-risk assessment applies to vaccines. The framework seeks to understand what the condition is, what the potential benefits are, and the risks. All of that is done in the context of what is known and what is unknown. There is a lot of uncertainty.

The US emergency use authorisation is critical to being able to be nimble in responding to emergency situations. For smaller outbreaks, the expanded access provisions can be used. This allows an investigational agent to be used with informed consent in larger numbers of individuals and requires the collection of very limited amounts of data, such as serious adverse events. However, expanded access is a very large undertaking and can be very costly.

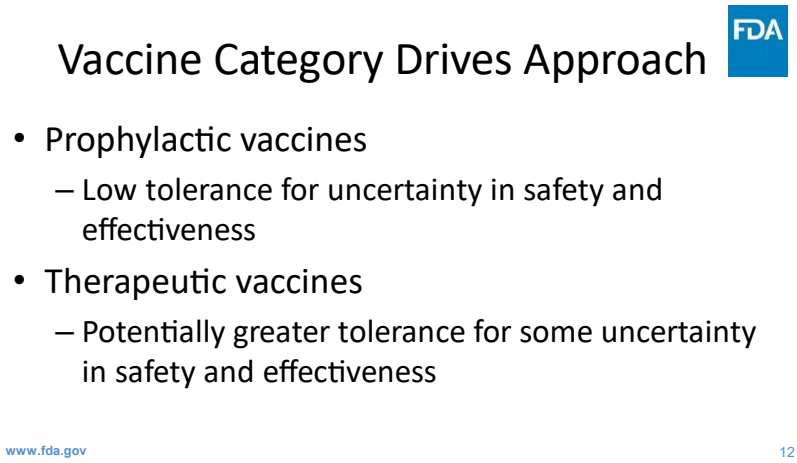
US Biologics License Application (BLA) approvals can be categorised into traditional full approvals, accelerated approvals based on surrogate endpoints, or if necessary, animal rule approvals. The animal rule allows for efficacy data in a qualified animal model. Safety data must be obtained in humans, supported by a pharmacokinetic study in humans. This pathway may be needed for some pathogens of concern.

Vaccines for cancer

The potential for vaccines that could be involved in primary prevention may be applicable to cancer in the context of: can minimal residual disease be eliminated? This is important because in many common cancers, people die from micro-metastases, rather than the initial disease, and that is something that potentially the immune system can be harnessed to eliminate.

With therapeutic vaccines, the FDA has potentially greater space for tolerance of some uncertainty in safety and effectiveness while the vaccines are being studied and ultimately gaining initial approvals. With prophylactic vaccines to prevent cancers, there must be a very low amount of uncertainty. For example, with HPV, indications are being added

for cancers that can be prevented because there is an incredible amount of safety information in the HPV databases, which meets the FDA's tolerance. Quality considerations for prophylactic and therapeutic vaccines are similar.



Vaccine confidence

There is the issue of vaccine confidence based on true uncertainty concern about unknown side effects and then there's exploitation of a situation. Vaccine hesitancy is complicated by the actions of people who have an economic or political incentive. Vaccination prevents disease and benefits public health. If there are great vaccines but people do not get vaccinated, it is a problem.

Panel discussion

Each panellist was asked to provide their reflections on increasing access and uptake for vaccines.

Dr Shelley Deeks, Deputy Chief Medical Officer, Nova Scotia Department of Health and Wellness, Canada

- It is important to consider how older adults are disadvantaged when it comes to vaccines. The oldest people are often excluded from clinical trials based on their living environment, such as long-term care. Frailty considerations have only recently started to be considered in trials.
- In economic evaluations, older adults are devalued as they have less life horizon, which has direct implications on cost-effectiveness results. This raises ethical questions.
- A report in 2023 looked at 34 countries and found that only three (France, Canada and El Salvador) had an expert in the field of aging in their NITAG committees. Excluding this type of expertise impacts the discussion and ultimately the recommendations made.
- In terms of inclusion in publicly funded programmes, perceptions by decision makers that vaccines for diseases in older adults are less critical impacts the allocation to this population.
- There are logistics challenges associated with delivering vaccines in long-term care settings and managing mobility limitations or cognitive impairments.
- There is a lack of awareness by the general public that vaccines are just as important for older adults as they are for children. This leads to lower demand.
- In order to increase access and uptake of vaccines in older adults, the biases which impact vaccination in this population need to be recognised and systematically addressed.

Dr Gowri Raman, Associate Director, New Technology Engagement, Patient-Centred Outcomes Research Institute (PCORI), USA

- Vaccine uptake can be increased through information sharing and engaging communities to overcome low vaccine confidence and hesitancy.
- Increasing access to vaccination, for example, pop-up clinics within school premises, instead of having to go to a local pharmacy, can increase vaccine uptake.
- Another example for increasing vaccination uptake in high-risk and hard to reach populations is by involving local communities in the vaccination efforts. For example, the National Black Church had an initiative to prevent COVID-19 in Black and Latino populations through a collaborative effort with the Centers for Disease Control and Prevention (CDC). They set up vaccination clinics in local churches and offered transportation to people who were interested in receiving the vaccination.
- PCORI's engagement awards through building capacity with stakeholders for comparative effectiveness research in particular groups such as the autoimmune population, pregnant and lactating women and care workers helps in eliciting their perspectives about vaccination. A common theme arising from these engagements was that increasing the information on safety and efficacy, specifically for the respective population, increased vaccine confidence.
- PCORI's ongoing comparative effectiveness research trial is currently evaluating the role of effective, tailored, and targeted messaging as well as shared decision-making with providers as compared to traditional messaging among long-term care workers to increase vaccine confidence and vaccine uptake.

Richard Hughes IV, Partner, Epstein Becker & Green PC, USA

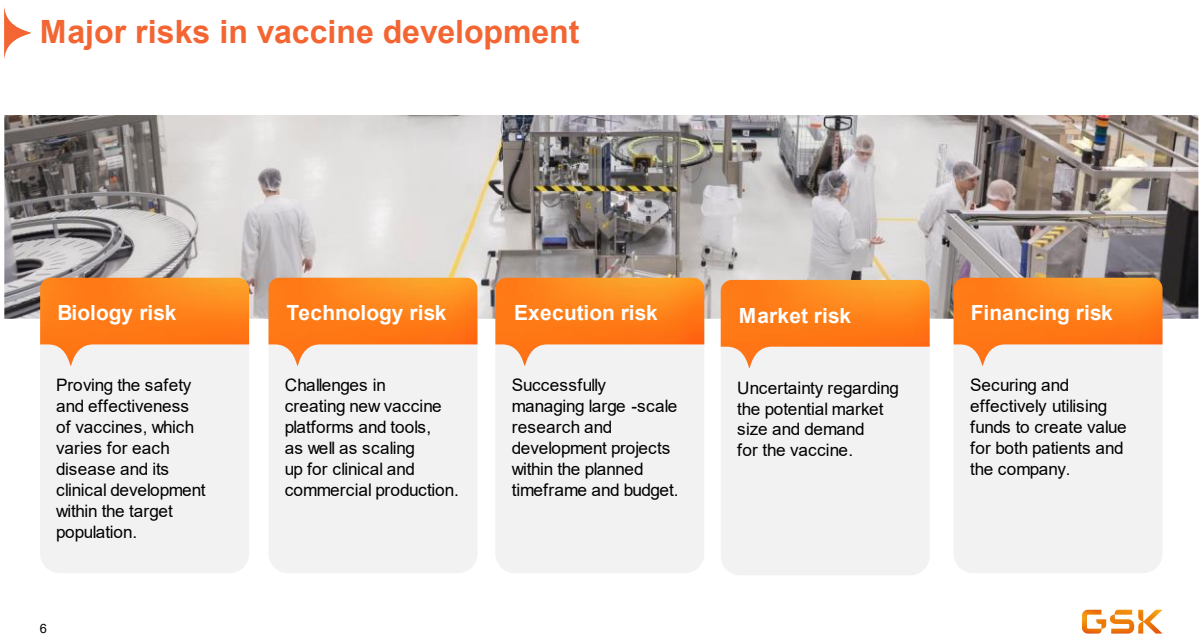
- Clarity when discussing therapeutic versus prophylactic vaccines is important. Policymakers are unclear on how they define products. FDA law does not have a definition of vaccine.
- The WHO will pre-qualify prophylactic antibodies as medicines rather than vaccines. This could have potential procurement implications. There was a European Commission proposal in 2023 to broaden the definition of vaccine to any medicinal product intended to elicit an immune response. In 2023 the Centers for Medicare & Medicaid Services (CMS) had a proposal for purposes of the Medicaid drug rebate programme (which excludes vaccines) to define vaccines as any prophylactic product.
- During the pandemic, CMS under part B that typically covers prophylactic vaccines, also included monoclonal antibodies both for prophylactic and therapeutic purposes.
- There was a recent court decision in the US which adopted the rationale that because a vaccine cannot prevent all transmissions, it is not effective, and that vaccines are forced medical treatment. There is a concerted effort by anti-vaccine activists to use the courts to perpetuate misinformation.
- Nine out of ten Americans have coverage for vaccines through either a public or a private source. However, if you are an uninsured adult (which applies to over 21 million Americans) there is no vaccine safety net like the one in the Vaccines for Children programme. The Bridge Programme, which was put in place during COVID-19 to provide that safety net, is being discontinued because there is no political will to maintain these investments.
- Everyone should have access to all vaccines regardless of the setting of care and source of coverage.

Session 2: De-risking vaccines development

Plenary presentation

Kumaran Vadivelu, Head, Vaccines Development, GlaxoSmithKline, USA

Vaccine development involves different technical and commercial risks (see slide below). For example, there is the biological risk of selecting the right target antigen, as well as the executional risk of successfully managing very large clinical trials, within planned budgets and timelines. Even if a particular vaccine is clinically effective, the bar for funding can be high, and even once funded, vaccine uptake can be unexpectedly poor due to low patient and healthcare professional awareness, vaccine hesitancy or apathy.



Think end-to-end process

Vaccine research and development is about evaluating the candidate for efficacy and safety to understand its full potential. It is also important to think about market access, as well as scaling up manufacturing for global deployment. Late-stage vaccine development is costly, time-consuming, and associated with high risk of failure. Today, developers are looking at close to a billion US dollars for every vaccine that is developed. In the early stages, a vaccine programme costs around $10 - $20 million, but as soon as the vaccine enters the clinic, this escalates exponentially. Approximately 10% of the candidates in the clinic proceed to licensure and launch; this is an area that needs de-risking.

Speed has a couple of advantages; it is not just about reaching the market, but to reduce the cost. Succeeding or failing quicker allows developers to relocate resources to more promising programmes, diversify targets and work on multiple technologies.

How to approach managing risk

The most powerful tool to manage risk is diversification i.e. working on multiple candidates with different targets and technologies at any one time. It is also about continuously investing in people to have the best talents managing these programmes and deploying digital technology to better monitor risks.

Having biomarkers that predict vaccine efficacy can speed up development and significantly reduce the risk. A good example is the meningitis B vaccine; if not for the availability of correlates of protection as a biomarker, it would not

have been possible to develop and license a meningococcal vaccine. Availability of biomarkers is also critical to expedite development of combination vaccines because it is not possible to re-run large efficacy trials again.

Managing market risk is about having a balanced portfolio with products and disease areas with predictability in terms of vaccine demand. Market risk is much more challenging when moving into new disease areas where the vaccine demand is unknown. Is it going to be restricted to a narrow population of individuals at increased risk, or is it going to be more routinely recommended and deployed in populations where the demand could be much higher? Early engagement with key stakeholders involved in national immunisation programmes is vital to get a better assessment of the potential vaccine demand, as well as to understand the pathway to market access for these products.

Vaccine health policy

The COVID-19 pandemic highlighted the critical need for equity consideration in vaccine health policy. There has been remarkable progress with six high-income countries incorporating equity as a criterion, but the gap is much wider for middle- and low-income countries. A recent Office of Health Economics (OHE) report, commissioned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (April 2024) reported that "Adult immunisation programmes are shown to be a highly effective investment for Governments and healthcare providers". This research provides evidence for adult immunisation programmes across ten countries and four vaccines showing that adult immunisation programmes offset their costs multiple times through benefits to individuals, the healthcare system and wider society.

No one would have believed at the beginning of the COVID-19 pandemic that there would be multiple vaccines coming through within 12 months. That was only possible because stakeholders were ready to take risks and flex the regulatory systems. Every stakeholder involved in vaccine development is now considering the learnings from that experience.

Panel discussion

Each panellist was asked to provide their reflections on de-risking vaccine development.

Sophie Sommerer, Director General, Biologics and Radiopharmaceuticals Drugs Directorate (BRDD), Health Canada

- When considering the concept of risk, thought needs to be given to what risk, whose risk, and who bears that risk, including the risk to societies and healthcare systems of not taking the challenge on.
- Key questions include: what is the level of risk tolerance? Who defines it? Who is accountable to whom? What is known and unknown?
- During the COVID-19 pandemic, uncertainty and risk had to be accepted, which was beneficial because it meant that regulators came together in a way they had not done before.
- The engagement regulators had with industry and the willingness to think differently are potential learnings to draw on from the pandemic.

Dr Robert Johnson, Director, Medical Countermeasures Program, Biomedical Advanced R&D Authority (BARDA), USA

- BARDA supports primary late-stage development of vaccines, therapeutics and diagnostics, focusing on areas where there is a public health need, but no sustainable commercial market.
- In many cases, licensed vaccines are competing against other public health priorities for procurement funding. The commercial market assessment is not the same as in other healthcare spaces.
- De-risking vaccine development can be enabled through companies interacting with regulators on the phase III trial design and incorporating regulators' feedback into the protocol in the way it was intended (not necessarily what is easiest for the company).
- It is equally important to identify and understand desirable post-approval attributes and build those into earlier development and phase III trial design as feasible. This both improves opportunities for uptake as well as decreases post-approval development costs.

Phyllis Arthur, EVP & Head, Healthcare Policy and Programs, Biotechnology Innovation Organization (BIO), USA

- Bringing together experts in government and industry during COVID-19 was a key factor in de-risking vaccine development.
- Manufacturing improvements and the use of other technologies were also key. This may have broader applicability and could drive more efficiency in manufacturing to improve yield.
- Flexible clinical trial designs and learning quickly to move into the next phase was an important agility used during the development of COVID-19 vaccines, along with recognition of the need to study diverse populations.
- FDA and CDC worked well together during the COVID-19 pandemic. Increased opportunities to discuss phase III clinical trial constructs with FDA, the CDC subject matter expert team and the implementation Advisory Committee on Immunization Practices (ACIP) team, all at once, would be highly valuable.
- If there is an infrastructure where adult vaccination is viewed as a standard of care, there will be more predictable demand.

Session 3: Regulatory challenges and metrics

Regulatory considerations – perspective from ANVISA

Dr Fabrício Carneiro de Oliveira, General Manager (Head Office) of Biological and ATMP, ANVISA, Brazil

A new regulation (RDC 846/2024) was published in Brazil in March 2024 to allow for the marketing authorisation of influenza pre-pandemic preparations. The regulation was needed both in recognition of the potential for larger influenza outbreaks and to update Brazil's regulatory framework for vaccines.

Surveillance for emerging pathogens

Influenza is in constant evolution and has caused many outbreaks around the world. WHO performs important global surveillance and has reported an increasing number of outbreaks, especially of the highly pathogenic influenza type A in poultry, wild birds, and wild animals. In March 2023, Chile confirmed human infection caused by the influenza A in the Antofagasta region. It was the third case reported in the Americas.

Globally, since 2003, there have been almost 1,000 human infections caused by the avian influenza A(H5) virus, including 458 deaths according to the WHO reports. There have also been recent reports in the US regarding the spread of H5N1 in cows, and the possibility of the presence of the virus in the cows' milk. It is impossible to predict whether the H5N1 virus will lead to a pandemic or not, however, there is a consensus that eventually a new influenza strain will emerge, which will bring challenges for treating the unprotected human population.

Pandemic preparedness

Considering the implications of a new pandemic for the health of the population, the economy, national security, and the basic functioning of a society as seen in the COVID-19 pandemic, Brazil started to better prepare itself for new pandemics and work on options to increase the velocity of vaccine development. The use of comparison data with existing vaccines, and surrogate endpoints which are reasonably likely to predict clinical benefit, will be important considerations for registering new vaccines. This approach will combine with post-approval effectiveness studies. During the COVID-19 pandemic, ANVISA had the possibility to issue emergency authorisations, which was a useful tool at the time but may not be the best tool moving forward.

Guidelines from EMA were the basis for regulation RDC 846, which established the ANVISA guideline for development and registration of pre-pandemic vaccines targeting zoonotic influenza strains. It was an important change because it allows ANVISA to authorise, using a platform, a vaccine that is not exactly the one that will be used in the occurrence of a pandemic but that can be quickly updated to the strain causing the pandemic. This regulation provides a fast-track pathway for approval and updates.

Regulatory reliance

Reliance can also be used to approve a product for pre-pandemic preparedness in Brazil. These are the reference authorities that can currently be relied upon for approval of any kind of product, including vaccines (in the future, others may be included if established criteria are fulfilled):

- I - EMA (centralised analysis processes), applicable to medicines and biological products.
- II - Health Canada, applicable to medicines and biological products.
- III - WHO, applicable to API, medicines and biological products.
- IV - European Directorate for the Quality of Medicines & HealthCare (EDQM), applicable for API.
- V - Swiss Agency for Therapeutic Products (Swissmedic), applicable to medicines and biologicals.
- VI - Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom: applicable to medicines and biological products.

- VII - US FDA: applicable to medicines and biological products.
- VIII - Therapeutic Goods Administration (TGA), Australia: applicable to medicines and biological products.

Reliance includes the verification procedure, where ANVISA will assess the evaluation of the reference authority to understand if the conclusions that could be applied in Brazil. This is critical for vaccines to consider the epidemiological situation of the reference country. The benefit is the reduction of costs for the developers and time for the vaccine's approval. If vaccines can be made available earlier for the population, there will be better results in terms of public health and economics aspects.

RDC 846/2024 - Next moves and Challenges

- First initiative of Anvisa is this direction - **platform strategy**
- Regulate this pathway for other diseases? Diseases? - Important to start the discussion
- Benefits – Reduction of costs for developers and time to the vaccine's approval.
- Communication–
  How to avoid misinformation, especially when we face "fake news" saying the vaccines are not tested
- Usage of reliance procedures during the updates consider ing the potential difference in the circulating strains between the countries.

Vaccine safety – meeting regulator, healthcare professional and community expectations*

Dr Rita Helfand, Senior Advisor for Science, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), USA

It is important to remember that infectious disease vaccines are given to otherwise healthy people, and there is a duty to detect even very small increased risks of severe adverse events that could be connected to vaccination/represent a safety signal. From the patient's perspective, the level of risk tolerated is defined by the risk and severity of the adverse event, the risk and severity of the vaccine-preventable disease, and the availability of alternatives to the vaccine.

Signal detection and assessment

Vaccine safety is an essential aspect through all phases of vaccine development. When studying tens of thousands of people in phase three clinical trials, very rare adverse events may still not be identified. Post-licensure monitoring aims to detect new or rare adverse events of clinical importance, monitor changes in patterns, identify risk factors and assess safety in special populations that may not have been studied in the clinical trials. It can be challenging to explain to the public and non-vaccine experts the distinction between signal detection (which may or may not represent a true safety issue) and the identification of a confirmed safety signal.

Signal detection requires a very high sensitivity, but with this comes a lot of background noise. Well-designed clinical or epidemiologic studies are then needed to evaluate a signal (e.g., hypothesis testing) to determine if there is confounding or it is a true safety signal. Per the WHO, at a minimum, countries should be able to conduct passive surveillance, in which healthcare workers, manufacturers, and the public can report any adverse event that occurs following vaccination, regardless of whether the adverse event is related to the vaccine.

For post-licensure monitoring, different complementary systems are utilised. As an example, the Vaccine Adverse Event Reporting System (VAERS) is a national US system co-managed by CDC and FDA that is set up to rapidly detect potential/possible safety signals. It can detect rare events but is not designed to determine causality. Other more robust safety systems, such as population-based and/or active surveillance systems are also used to determine if there is an elevated risk after vaccination. For instance, CDC has the Vaccine Safety Data Link, which is a collaborative project between CDC and 13 healthcare organisations that monitor millions of people in the United States, and can conduct near real-time rapid analyses with robust statistical methods to detect safety signals, and determine if a genuine vaccine-associated risk exists. Additional special studies are conducted as needed to evaluate and better understand potential safety issues.

In the US, multiple federal agencies work together on vaccine safety. For instance, FDA also has active surveillance systems, and CDC collaborates very closely on those because signals detected from more than one system, with different strengths and limitations, can increase the confidence that a signal represents an actual vaccine-associated risk. International collaborations are also important, such as VigiBase, WHO's global passive surveillance system.

For new vaccines, when considering what specific adverse events may be of special interest (AESIs) to monitor closely, regulators and public health professionals are considering things such as anaphylaxis, proven associations with a known platform or adjuvant, potential effects based on the immunopathogenesis of the disease, events observed in animal models or preauthorisation clinical trials, topics of previous interest (e.g., death after vaccination), events specific to special populations, unpredicted events, and if using a live attenuated vaccine, events related to viral replication.

For COVID-19, strong complementary vaccine safety systems were in place to rapidly detect and assess/evaluate safety signals. For instance, in the United States, this was the most intensive vaccine safety monitoring that CDC had ever carried out. It helped inform policy and clinical considerations in near-real time, enabling systems to be adapted as needed. Reporting of adverse events can have a real effect on the confidence and use of vaccines.

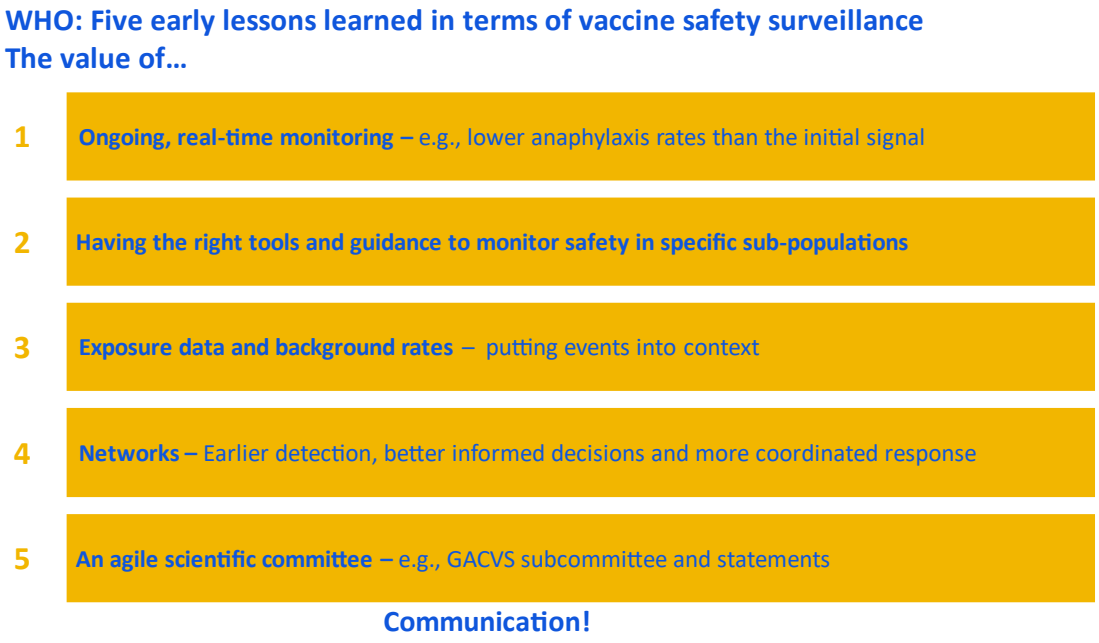
Examples were presented of initial signals that were found not to be a safety concern (e.g., after reviewing data that had resulted initially in a pause in vaccination from healthcare workers who had absenteeism due to intense flu-like symptoms after the AstraZeneca COVID-19 vaccine, it was found that people had mild to moderate symptoms that were consistent with what was identified in the clinical trials and the findings did not constitute a new safety concern) and signals that were found to constitute a safety signal (e.g., Thrombosis with Thrombocytopenia Syndrome after the

AstraZeneca and Janssen COVID-19 vaccines and myocarditis/pericarditis after the mRNA vaccines). They also demonstrated the importance of conducting benefit risk analyses.

Challenges were discussed, such as the varying quality of surveillance in different countries and settings, the multiple vaccines being used simultaneously, and the rapid immunisation that could lead to background rates of an illness or death potentially being considered an adverse event following immunisation.

Key elements of safety surveillance

Ongoing real-time monitoring, having the right tools to monitor special populations, exposure and background rates, having networks to help better inform decisions, and having an agile scientific subcommittee are all important elements of safety surveillance (see slide below) during a pandemic. Once risks have been identified, it is critical to communicate this quickly, openly, and transparently to advisory committees, public health, clinicians, as well as to the public.

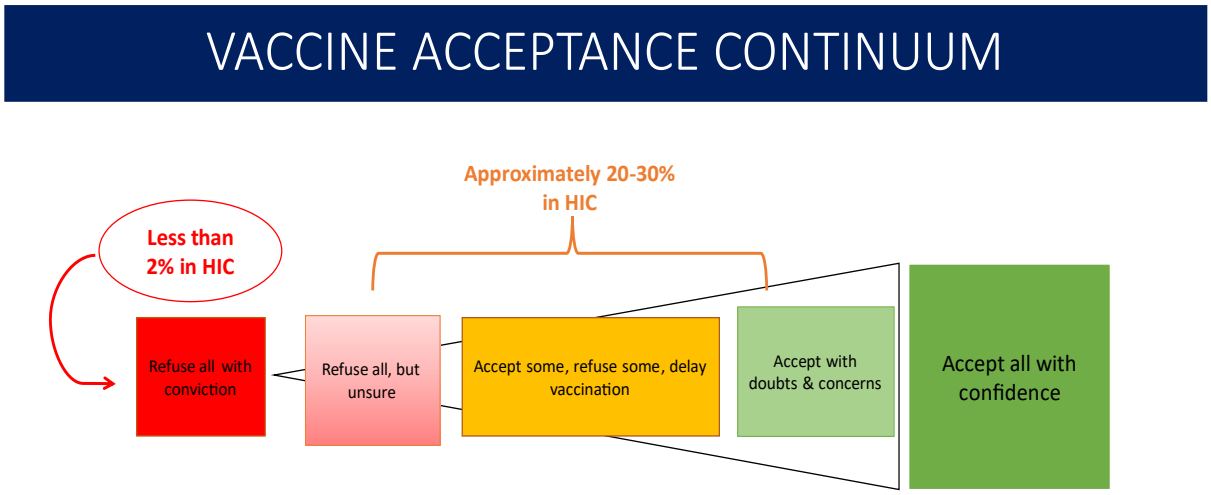


**The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the CDC. Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC.*

Vaccine safety and risk communication – meeting regulator, healthcare professional and community expectations

Prof Eve Dubé, Professor, Department of Anthropology, Laval University, Canada

Vaccine acceptance levels are on a continuum (see slide below). At one end are people that accept all vaccines with confidence, and that is most people in most high-income countries. At the other end of the continuum, are a small minority of people that are vaccine refusers, including vocal vaccine opponents. In the middle are the vaccine hesitant. Those people can accept vaccines, but with important concerns and doubts. They could delay vaccination, or they could select some vaccines and not others. That is the group that is the most important for public health because it represents a larger group than vaccine opponents, and if their concerns are not well addressed, they are the ones at risk of becoming vaccine refusers.



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Vaccination decisions

People make vaccination decisions in the wider social world setting. Vaccination decisions are complex and multifactorial. There are multiple theoretical models to explain those determinants. One of the most well-known is the 5C model (Betsch and al., 2018): confidence, complacency, constraints, calculation and collective responsibility.

Vaccine safety concerns are important drivers of vaccination decision. Indirect exposure to uncommon and rare adverse events can decrease the acceptance of vaccines. Indirect exposure to unproven false serious adverse events also decreases vaccine confidence, but having personally experienced a common adverse event does not impact someone's intention.

Studies have also shown that if someone is hesitant before getting vaccinated, they are more likely to report an adverse event after immunisation and are likely to report these adverse events as more severe. Passive surveillance systems for adverse events after immunisation (AEFI) could therefore be influenced by whether people are highly hesitant before vaccination.

Risk perception and communication

Experts and the public perceive risks differently. While experts conduct evidence-based analysis, the public is often driven by emotion. Vaccine safety communication aims to influence risk perception and build trust towards health authority recommendation. Communications should empower people to make informed decisions about vaccination and support those delivering vaccines to have access to timely evidence-based information to help assess people's concerns and respond to them.

For most people that are confident toward vaccine safety, there is minimal information that is needed. Managing pain and anxiety and explaining the common adverse events to expect after vaccination is important too. For example, many parents are not aware of the possible rash for a measles vaccine that occurs 10-12 days after vaccination. The approach however is different when speaking to a vaccine hesitant person and strategies using motivational interviewing techniques can be really effective.

At the population level, it is important to plan and prepare vaccine communications as well as we plan and prepare vaccine clinical trials or regulate the vaccine. The vaccine communication team is often separate from the vaccine scientists or experts, which can make the vaccine messaging not aligned with the science. It is also important to identify potential threat to vaccine safety perception in the public and to be prepared. Regular surveys, focus group discussions and social media 'listening' are all good ways to monitor vaccine acceptance signals.

Framing the message

Negative language tends to stick in people's minds. Half of all adults do not have the literacy skills to interpret complex mathematical information. Even when understood, the same information in different formats can be interpreted differently. For example, stating that 10% will have a fever is perceived as less risky than 'one out of ten' because ten people are easier to visualise, whereas 10% is abstract.

Openness and transparency are key. It is much easier to create a myth than to debunk a myth, as people just remember the myth, or the potential association, and they do not recall the scientific explanation. It is important to fill the gap and to lead with the facts, not the myth.

Emotions are very influential in how people perceive vaccines, perceive vaccine risk, and how people assess vaccine information, even if they completely understand the facts. Social media stories are powerful because they are authentic, have a narrative, and it is easy to identify with the person sharing the story. The main tool of the vaccine opponent is to share stories about how vaccines are harmful. Therefore, it is important to plan and prepare a vaccine safety communication, use an evidence-based approach and to assess public reaction.

What are the advantages of and potential barriers to regional alignment of regulatory review models for vaccines?

Company view

Andrew Emmett, FDA Liaison / Executive Director for US Regulatory Policy & Global Intelligence Pfizer, USA

All stakeholders recognise that the COVID-19 pandemic was an extreme, urgent situation, and a lot of the approaches employed during the pandemic may not be sustainable in the long run. However, it is also recognised that it would be a missed opportunity if some of the efficiencies gained could not be further leveraged, not only for future pandemic situations, but also for routine regulatory review of vaccines and other medical products.

Regulatory agility

The retrospective study on 'Regulatory agilities impacting review timelines for Pfizer/BioNTech's BNT162b2 mRNA COVID-19 vaccine' sets out the experiences of 74 countries during the pandemic. Review times were much shorter and strongly influenced by reliance practices. Platform approaches, labelling and CMC requirements were particularly agile. Implementing all these agilities in tandem has a synergistic approach of creating a more dynamic review process.

Regulatory reliance

The use of reliance pathways is gaining momentum, with a range of practices, starting with basic collaboration and information sharing, building up to reliance and work sharing, and ultimately to full recognition. The benefits of using these approaches include not only more timely access to safe and effective and quality products, but more efficient use allocation of resources, both on the industry side and the regulatory authority side.

It is important to recognise that there are also barriers to reliance practices. One of those is demonstrating the sameness of a product across different regions, even if it comes from the same production line, being able to demonstrate that it is equal. In addition, making sure that there's clarity on access to regulator-generated documentation and the documentation that was submitted to the reference authority. It is important to have very clear criteria on the processes for reliance procedures, documenting what is required, when, and how it is going to be used in the assessment.

Technology

International collaboration was a hallmark of the pandemic, facilitated by real-time exchange of data. There is movement towards a cloud-based submission architecture as a key enabler for reliance pathways. Agile platform technologies are emerging that can be rapidly programmed and repurposed to counter emerging pathogenic threats and other areas of unmet medical need.

Electronic labelling

One of the key learnings from the COVID-19 pandemic was that electronic labelling, particularly QR codes on the COVID-19 vaccines, provided patients and physicians with the opportunity to have the latest information much sooner. Paper-based systems take several months for leaflets and prescribing information to make it through the system. They are hard to read, are not customisable and use about 11 million trees per year to produce.

Vaccine strain selection

The process for respiratory vaccine strain selection has been suboptimal. Newer approaches are emerging that can lead to more rapid manufacturing scale-up and may provide additional time before making the decision on which strain until later in the process, with hopefully a higher likelihood of having a match and better public health outcomes.

Conclusions

Regulatory agilities can collectively achieve more efficient regulatory systems

- Global reliance pathways to strengthen international cooperation and leverage capabilities worldwide
- Platform approaches allow for more timely public health emergency responses, streamlined vaccines development, and more efficient use of resources to develop next generation vaccines
- E-labeling and digital systems strengthening can promote timely communication of accurate data and product information
- Global alignment on an agile, timely strain selection and confirmation process to promote greater likelihood of a match to circulating strains of respiratory diseases

What are the advantages of and potential barriers to regional alignment of regulatory review models for vaccines?

Regulator view

Dr Claus Bolte, Chief Medical Officer, Swissmedic

Advantages and barriers

There are advantages and barriers to regulatory review alignment (see slide below), such as the Access Consortium work sharing and Project Orbis simultaneous review. The major barrier is building trust, not just within an organisation, but also with another agency in a different time zone; the agency's assessment methodology, procedures, and culture may be unknown. The major advantages of using such alignment pathways are sharing of resources and expanding expertise to learn from each other.

Regulatory Review Alignment

Advantages	Barriers
Efficiency: Reduced workload due to splitting review / modules between agencies	Building **trust!**
Sharing of resources and **expanding expertise** across jurisdictions	Increased **coordination** effort including working across several time zones
1st-wave-agency positioning with a large population	Creating consolidated work-sharing **procedures**
Faster assessment time and **shorter** submission gap	**Peer review** based on «**foreign**» assessment report

Timelines

Data published by CIRS on timelines for six leading regulatory agencies [the EMA, US FDA, Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA)] shows the submission gap and review times for each agency (see CIRS R&D Briefing 93). These metrics confirm one rationale for developing collaborative review efforts. For new active substance (NAS) applications participating in either the Access Consortium or Project Orbis, both the submission gap and regulatory assessment times were significantly reduced (see CIRS R&D Briefing 88).

Industry perceptions

An industry perception survey highlighted a faster time to market, reduced duplication for industry as well as regulators, and a reduced submission gap as key reasons to participate in an Access Consortium review. Reasons given for not participating included a perceived risk of divergent decisions, the influence of one authority on another, or not being able to identify a suitable candidate. Recommendations for improvement were to ensure predictability, increase guidance and transparency, streamline processes, enhance communication and maintain flexibility. These recommendations are reflected in the Access Consortium Strategic Plan 2021-2024.

Regulator considerations

When there is an enormous public health impact, regulators can move very rapidly in terms of joint or collaborative review efforts, especially when developments are based on established technology. However, if the technology is novel, or when smaller subsets of a population are involved, collaborative review tends to take more time. Although regulators are more aligned than ever before, it is important to remember that for a collaborative review, each jurisdiction will decide on its own whether to approve or not.

Session 4: Are current health technology and NITAG assessment models for vaccines fit for purpose?

Plenary presentation

Prof Lotte Steuten, Deputy Chief Executive, Office of Health Economics (OHE), UK

Compared to many other interventions, vaccines accrue a relatively big part of their value outside of the healthcare system. The current HTA methods are especially disadvantaging vaccines by not comprehensively assessing their broader value.

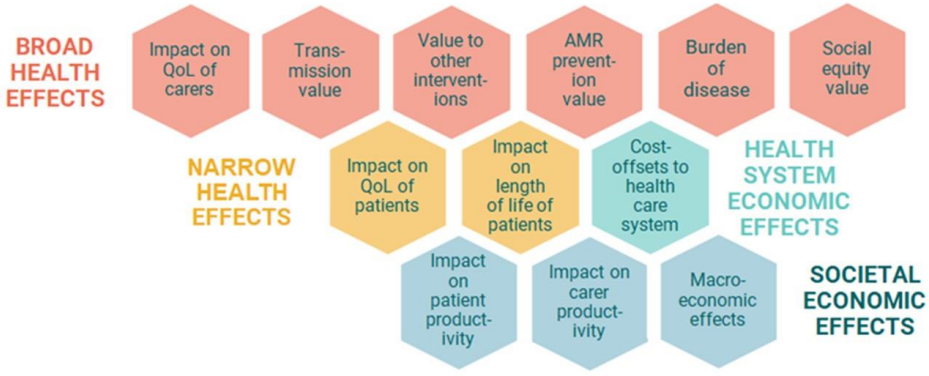
Value elements

Caregiver productivity goals, caregiver quality of life, and macroeconomic effects, which were all important with COVID-19, are all relevant elements in determining broader value. In addition, some estimates show that the actual opportunity cost of hospital bed days rather than the accounting costs are higher than typically assumed, particularly in the times of high pressure on healthcare systems.

There are several frameworks which look at the broader value of vaccines. When conducting value assessment, the impact on mortality, on quality of life, and the cost offsets to the healthcare system are central to the vaccination framework. In addition, there can be broader health effects for example impact on quality of life of carers, transmission value, herd immunity and social equity (see slide below).

OHE

What do we mean by "broader value" of vaccines?
A value framework for vaccines



Key: QoL = Quality of Life; AMR = antimicrobial resistance.

Source: Bell E, Neri M, Steuten L. Towards a Broader Assessment of Value in Vaccines: The BRAVE Way Forward. Appl Health Econ Health Policy. 2022;20(1):105-117.

Most HTA agencies, by choice, do not consider a broader societal perspective in the value assessment of technologies including vaccines. However, some of them will consider some of these broader value elements in their deliberations, without necessarily incorporating them directly into the cost-effectiveness analysis.

Incorporating value into the economic evaluation

Does all of this broader value have to be incorporated into the economic valuation in a quantitative way, or can it be used in a more qualitative way? What would it mean for cost-effectiveness thresholds? A survey of global industry experts identified five elements as important:

- Transmission value.
- Productivity and quality of life of the people that are vaccinated, as well as their caregivers.
- Prevention of antimicrobial resistance (AMR).
- Cost offsets within the healthcare system.
- Macroeconomic effects.

Demographic shifts

With aging populations in many places of the world, it is important to keep our citizens as healthy and as productive for as long as possible. There is a paradigm shift needed, and adult vaccination can play a very fundamental role, but awareness about the value of vaccines is low.

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) commissioned OHE to do a study on the social economic value of adult immunisation programmes. The countries included in the study were mostly higher and middle-income countries because they had vaccination programmes in place. The study found that the value generated by adult immunisation programmes offset their cost multiple times by preventing and reducing morbidity and mortality, reducing health care costs and by increasing productivity, social equity, and delivering other broader societal values. Monetising the full spectrum of benefits showed that adult vaccines can return up to 19 times their initial investment to society.

Summary

Now, more than ever, healthcare systems must invest in strategies to cope with unprecedented and growing demand. Prevention must be at the centre, and robust adult immunisation programmes are a fundamental component of effective prevention. Given their favourable benefit-cost ratios, expanding access to a broader adult population may generate even more value particularly from a societal perspective. While existing evidence shows that the value of adult vaccination is reliably high across different contexts, data gaps remain for some of the broader elements of the value of immunisation programmes, indicating a need for ongoing research.

Panel discussion

Each panellist was asked to provide their reflections on current health technology and NITAG assessment models for vaccines.

Academic viewpoint – Peter Neumann, Centre for Evaluation of Value and Risk in Health, Institute of Clinical Research and Health Policy Studies, Tufts University, USA

- A review of published literature on the cost effectiveness of vaccines shows that most studies omit wider productivity and economic benefits in their evaluations.
- The benefits of an effective vaccine accrue not only to patients but also to caregivers, family members and to wider society in terms of economic benefits. However, these benefits are harder to measure.
- Payers often view wider societal factors as falling outside their remits. There is also a perspective held by some that if the wider benefits are measured, this will support high prices.
- Value assessment can be important inputs to considerations of pricing, reimbursement, affordability and access, but should be conducted by independent bodies.
- There are important new methodological advances in terms of value measurement; for example, financial risk protection, which is the idea that some of the benefits of effective interventions are not direct health benefits, but rather avoiding financial difficulty.
- Improvements in the measurement of patient preferences are also being made.

Company viewpoint – Craig Roberts, VP, Outcomes Research, Merck, USA

- NITAGs vary in their remits, including whether or not they have funding responsibility and how they connect with the HTA body in their country.
- To achieve an evidence-based public health recommendation as soon as possible after regulatory approval, there needs to be information exchange. Structured processes for communication allow for sharing of not just clinical data, but economic data, epidemiologic data, and cost-effectiveness data.
- Most of the analyses by NITAGs is confidential and only a summary is published in the minutes of meetings.
- Not everything that counts can be counted, and not everything that can be counted counts.
- Ease of implementation and simplicity of recommendations are valuable.
- NITAGs need to continue to advance the methods of assessing adult vaccination. Adults are different than children. Children age out of risk. Adults age into risk.
- Not all of the information is available on the day of launch. Assumptions have to be made and then continuous monitoring of effectiveness post licensure.

US ACIP viewpoint – Dr Melinda Wharton, Executive Secretary, Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention, USA

- In the ACIP charter, the criteria for evaluation of vaccines for prevention of infectious diseases includes disease epidemiology and burden of disease, vaccine safety, vaccine efficacy and effectiveness and the quality of evidence reviewed (which should perhaps be changed to ‘certainty of conclusions’).
- Economic analyses and implementation are operationalised through the recommendation framework ACIP adopted in 2018 which has seven domains: public health problem, benefits and harms, values, acceptability, resource use, equity, and feasibility.
- The cost-effectiveness of products is assessed, but there is not a cost-effectiveness cut-off for what ACIP would recommend. The committee's primary focus is preventable disease burden and the expected efficacy and safety impact of implementation of a vaccination programme.
- Convening ACIP working groups earlier in the process would allow for reflection of issues arising during clinical development and the committee could provide some feedback. This would not be binding for future decisions post-licensure, but engagement on products where there is a lot of uncertainty would be helpful.

European NITAG viewpoint– Dr Jaime Pérez-Martín, Head Prevention Service, Murcia Health Department, Spain

- Increased collaboration between NITAGs in Europe is needed. The experience of NITAGs working together with the European Centre for Disease Prevention and Control (ECDC) for evidence review is positive, but every country still needs to have their own recommendations.
- One of the main challenges that NITAGs have is accessing expertise on the wide range of new technologies and approaches. Being able to evaluate the benefits of vaccines not traditionally evaluated, e.g. against antibiotic resistance or avoiding the long-term consequences of infectious diseases, could contribute to more precise evaluations by NITAGs.
- With very severe disease of low incidence, it is difficult to evaluate with traditional assessment criteria, especially for cost-effectiveness, so flexibility is needed.
- Public health recommendations were historically quite general and applicable to the whole population. Today the approach is more on personalised medicine and the NITAG has to make recommendations specific to different groups, which is more difficult and takes more resource.
- NITAGs play an important role against vaccine hesitancy; when NITAG recommendations are robust and well supported by evidence, vaccine policies should be easier to follow and reduce public doubt.

Session 5: Roundtable discussions: Priority research areas and how to address policy challenges

Workshop participants were assigned to a roundtable group and provided with a handout of background information and questions for discussion (developed by CIRS). The Chairs and Rapporteurs of each roundtable were asked to facilitate and document the discussion, respectively. The Rapporteurs then fed back to all workshop participants in the main plenary session.

Roundtable A: What collaborative evaluation models and metrics should be developed to support vaccine regulatory or funded access?

Chair: Prof John Lim, Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Senior Advisor, Ministry of Health, Singapore

Rapporteur: Saiza Elayda, Associate Director, Global Regulatory Policy, Merck, USA

Metrics

There is currently very little vaccine-specific information on regulatory and HTA timelines/approvals for vaccines compared with medicines. By considering the following questions, the roundtable group identified key areas for potential metrics on vaccines as well as the purpose of such metrics.

Question	*Key Areas*	*Purpose*
What are the key areas that should be collected/covered to provide value added information and provide insight into the changing regulatory landscape for vaccines?	What do review processes look like? Are there average timeframes for review?	Transparency
What are the key areas that should be collected/covered to provide value added information and provide insight into the changing NITAG/HTA landscape for vaccines?	Horizon scan of NITAG/HTA frameworks. Data reviewed/submitted for review.	Help in understanding of differences and similarities.
Which information on regulatory approval times and NITAG/ HTA success by type of vaccine technology and target disease type?	Horizon scan of reg approvals vs NITAG recommendations.	Understanding of what could cause delays in market access.
Which information on extent of use of facilitated pathways for vaccines, and parameters considered by regulators who grant facilitated pathways?	Horizon scan of what pathways are available for vaccines.	
In gathering metrics, would it be valuable to consolidate information on national processes and policies on funded vaccine coverage?	Data submission requirements.	Understanding of the similarities and differences in requirements (It may not be helpful to look at these types of issues until there is a common understanding of the lexicon for the regulatory framework)

Collaborative evaluation models

The group also considered the following questions on collaborative evaluation models for vaccines. Below are the key points from the discussion.

Is there a need for more structured mechanisms for collaborative evaluation of vaccines between regulators?

- Horizon scanning could be done to understand evaluation processes, but not open ended. First, look at the more basic types i.e. infection disease, but also therapeutic vs prophylactic.
- Look at various countries' perceptions of vaccines and how this may influence evaluation.

Many emerging market regulators will struggle to have the technical capacity for regulatory review of new vaccine platform technologies such as mRNA and viral vector vaccines – how can major regulators, industry and international foundations support this?

- Case studies of how to support low and middle-income countries (LMICs) from COVID-19, RSV, Ebola.
- Explore how reliance can be used to help regulators in their frameworks and joint assessments, but also in how to educate health systems and disperse information to the general public, especially for new technology.
- Major regulator support for WHO and other NGOs (Gates Foundations, CEPI) for capacity building in LMICs. Understanding of the kind of issues impacting how to apply reliance processes to vaccines is needed.

Recommendations

The group made the following recommendations for future work or research to support collaborative evaluation models and metrics for vaccines:

- Horizon scan of the definition of "vaccine", including how the term is communicated in society. Without a common lexicon, it's hard to have further discussions on what metrics could be utilised. A definition that can be future-proofed is needed, but this should not be so prescriptive that any new future technology is excluded.
- Horizon scan of vaccine regulatory, HTA and NITAG frameworks. Why, outside of the COVID-19 pandemic, is it often taking longer to evaluate vaccines versus other products?
- Evaluate reliance use and challenges, following horizon scanning on the landscape of vaccine definition and applicable regulatory, HTA and NITAG frameworks. An understanding is also needed of the specific issues impacting how to apply reliance processes to vaccines as opposed to other drug products.
- Bring stakeholders together to discuss the business case for a company to continue manufacturing a vaccine when patients are not receiving it.

Roundtable B: How do we evolve the regulatory system to accommodate new vaccine technologies and challenges?

Chair: Dr Supriya Sharma, Chief Medical Adviser, Health Canada

Rapporteur: Silvia Aiolli, GRA Therapeutic Area Head mRNA Vaccines, Sanofi, Italy

The group considered the following questions. Key points from the discussions are summarised below.

Should therapeutic vaccines, including cancer, be regulated as drugs or vaccines?

- Inconsistency across different jurisdiction in the definition of mRNA vaccines, neither for preventative nor therapeutic vaccines. This has implications for regulatory review, IP and reimbursement aspects.
- For well characterised mRNA that are similar to small molecules, but the mechanism of action is similar to vaccines, there may need to be a hybrid approach to cover both aspects.
- No clear definition of vaccines in different jurisdictions (EU vs US). Who reviews them? E.g. CDER vs CBER
- Cluster medicinal products according to their therapeutic area, regardless of the manufacturing technology. However, this may take a lot of time - could be done as a regionalisation classification?

How could individualised vaccine therapies be regulated when every patient will receive a unique product?

- Regulatory framework needs to be transparent and predictable.
- mRNA cancer vaccines: are they really vaccines or INATs (Inhaled Nanocarriers with Antisense Therapy)? Calling them vaccines can create false expectations in the general population.
- Safety database of therapeutic vaccines is different (smaller, aligned to therapy area) to the one for preventive vaccines.

Please document information on the types of evidence required by regulators e.g. clinical trials, natural vs challenge trials, immunological correlates.

- The regulatory framework should not be too strict/rigid - keep the agility.
- Is the current balance of evidence appropriate?
- Correlate of Protection (CoP): Regulators more open to CoP rather than running larger efficacy studies. There is a lack of consistency across jurisdictions e.g. for COVID-19, CoP accepted in EU but not in US. It would be beneficial to have a more consistent approach, though full global harmonisation may not be possible. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) might be a supportive model, but time is a problem. Also, WHO can have a role, considering LMICs.
- mRNA peculiarities: lot-to-lot (L2L) study not needed for mRNA because it is well characterised.
- Human challenge studies: Can they be used as pivotal studies? Not at present – perhaps on a case by case basis. Companies should go for scientific advice. Safety database should be established anyway.
- How are regulators discussing harmonisation? Full harmonisation is challenging e.g. paediatric.

What is needed to develop and better align regulatory approaches for new vaccine platform technologies e.g. mRNA and viral vector vaccines?

- Need a platform guidance that is coherent across jurisdictions. The first draft platform technology guidance from FDA for CMC and non-clinical (toxicology studies) is a positive step; could expand in a stepwise approach to clinical safety, change control management for lifecycle management and post-approval changes (PAC). However, not all countries are at the same stage for endorsing the platform approach (as it might be a disincentive for conducting clinical trials in a given country).
- PAC protocols should be implemented also outside EU/US.
- Can regulators look at the comprehensive data package coming from a platform technology?

Are approaches for the use of real-world evidence (RWE) in supporting vaccine label extensions to different populations clear enough?

- No, outside of the COVID-19 pandemic. ICH is taking this issue up as a concept paper. However, even for COVID-19, there are not many RWE data supporting label changes.
- Regulators ask for full dataset package, which might not be easy to get.
- Vaccines could be the most appropriate products to support use of RWE data.
- In Brazil an external working group was created and published a guidance on how to design and collect data from observational studies to support development of all drugs including vaccines. This is a good example to be followed by other countries.
- Recommendation to use RWE as pivotal data; this is especially useful for medicines used off-label.
- Agencies can have pilot projects, like the one currently ongoing in FDA.

What role do regulators have in communicating benefits, risks and safety issues with vaccines?

- COVID-19 pandemic was an important experience and gave an opportunity to 'humanise' regulators.
- Communication must be managed at the top level. Anthropologists and social scientists should be involved.
- Proactive communication is necessary. There must also be a rapid response when an issue is bubbling up.
- Outside of an emergency, communication can be more challenging. What is the real role for regulators in this besides publishing the assessment report, labelling etc.?

Recommendations

The group made the following recommendations to evolve the regulatory system to accommodate new vaccine technologies:

- Harmonised definition of preventive vaccine vs therapeutic vaccine is needed.
- Reflect on the size of safety database needed for therapeutic vaccines compared to preventative vaccines.
- Need greater clarity on use of human challenge studies, not only for understanding the risks, but also for use as pivotal data for a given product.
- Need platform guidance coherent across jurisdictions, starting from CMC and toxicology. Expand in a stepwise approach to clinical safety, change control management for lifecycle management and post-approval changes. Not all countries are at the same stage of acceptance for platform technology, and this may create delays in access.
- Expand use of RWE for vaccines. Leverage the RWE process that Brazil has put in place as a good example for other countries and in support of ICH concept paper in development.

Roundtable C: How can we ensure that vaccine health economic assessment/HTA is fit for the future?

Chair: Prof Hans-Georg Eichler, Consulting Physician, Association of Austrian Social Insurance Institutions

Rapporteur: Joseph Kelly, VP, Global Pricing and Market Access Head, Vaccines, GlaxoSmithKline, USA

The group discussed the following questions and highlighted key considerations and potential solutions:

Questions	*Key Considerations*	*Potential Solutions*
Value assessment of vaccines - what approaches to include? which outcomes other than direct health benefits should be explored to support funding decisions?	• Policy makers need to communicate what data would be needed to allow value to be recognised (both broader societal & traditional direct value) – over short & longer term. • Manufacturers want to know what population will be included in recommendations - NITAG need to see the supporting evidence.	• Earlier engagement – a deliberate and iterative formal process to allow exchange of fundamental information between manufacturers, NITAGs and HTAs. This should happen as soon as feasible to allow input into evidence generation plans. • Equity should be formally considered to recognise the consumer/patient perspective.
Is there a need for greater alignment of the evidentiary data required for vaccines by regulators and payers could lead to faster funded access and deployment?	• NITAG capacity a key challenge to solve – in new era of vaccines, this may be under further pressure.	• Simplify if possible - review stepwise, sequenced approach to assess if efficiencies can be achieved (e.g. Canada/Australia). But be aware of potential for 'contamination' and ensure clear lines of separation/independence in place. • Greater investment from ministries of health/finance in NITAG resource. • Consider potential for public/private partnerships – integrity and independence must be maintained. • Petition government for greater funding – demonstrate the value of a well-resourced NITAG.
Greenspace thinking: If we could change the world, what could we do to drive quicker access/benefit of vaccination?	• Consider keeping approaches that worked during the COVID-19 pandemic. • How to do a partnership between NITAGs – what travels and what doesn't? • Include the patient perspective – patient advocacy groups can help to build political will	• Regional collaboration on better information sharing. • Greater use of equitable tiered pricing for lower income nations – ensure considerations on inappropriate international reference pricing are addressed. • Equity should be included in HTA – consider existing solutions & explore novel approaches e.g. distributive cost-effectiveness analysis, equity weights, quality measures.

The group made the following recommendations for future work/research to evolve vaccine health economic assessment/HTA:

- Ensure there is a formal deliberate and iterative process for information exchange between manufacturers, NITAGs, and HTA bodies, including the patient perspective. Early engagement is key to allow inclusions of endpoints in the clinical development plan for phase 3, but also allowing an iterative process as the data matures.
- Support increased NITAG capacity and investment in talent / skills for NITAG reviewers. The independence of the agency must be maintained, with management of potential for perception of conflict of interest.
- Petition governments for greater funding in terms of NITAG resource, and talent retention.

Session 6: Future vaccine technologies and deployment

Future vaccine development – Non-RNA perspective

Pascale Vintézou, Vice President, Vaccines GBU Head, Sanofi, France

Scientific advice

It is generally accepted that seeking early scientific advice with relevant bodies is valuable to support development. But could there be a greater role for early engagement?

In the last decade, many regulators have formalised the opportunity for developers to seek scientific advice on vaccine development strategy, with agencies such as EMA and FDA offering more opportunities for engagement from early in development through to the registration of the product. There are fewer opportunities to seek advice from HTA bodies or NITAGs. With new approaches to R&D including artificial intelligence and digital tools for evidence generation, it is even more important than ever to engage regulators and other relevant bodies early in development.

The new European Union Regulation on HTA, which will apply from January 2025, introduces the option for joint scientific consultations, including for vaccines. It will be possible to opt for joint scientific advice with EMA and HTA bodies, or to only involve a certain number of HTA bodies. For joint advice, EMA and HTA bodies will have a joint meeting, but will provide their advice separately in parallel. The HTA bodies will consolidate their response into a single advice. There are still several questions associated with the rollout of the HTA Regulation, including how many advice procedures will be conducted each year.

The NITAG is a key actor missing from scientific advice consultations. NITAGs play a critical role for recommending vaccines, therefore, industry, NITAGs and HTA bodies will need to continue to work together and find adequate forums to exchange early enough on their respective perspectives.

Data generation and data sharing

Regulators and HTA bodies have been working together for decades, however, their collaboration is evolving to increase the exchange of information. This relationship is important to make sure there is access to innovative vaccines in a timely manner. It is also important to optimise the generation of evidence relevant to both regulators and HTA bodies. The European industry wish to maintain distinct, separate and well-defined roles for the regulator and national HTA body; there should be cooperation and collaboration between the two stakeholders, but processes must remain separate.

Regulatory and funding pathways

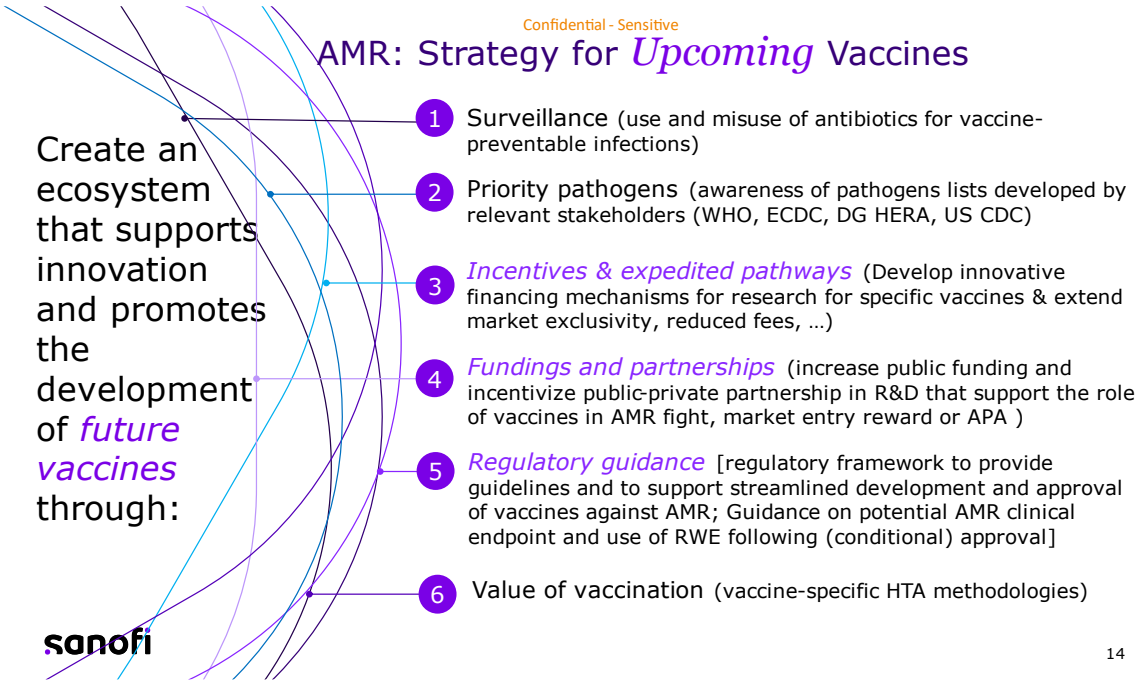
New regulatory pathways and funding models are needed to support the development of vaccines targeting an unmet medical need for a disease with low prevalence. There are existing tools which can be leveraged, including scientific advice and special designations, which speed up review and assessment, but more are needed.

Managing uncertainty

In the last decade, including during the COVID-19 pandemic, new ways to generate evidence have been introduced and this is creating some uncertainty. To address and manage uncertainty, stakeholder engagement, transparent communication, education, and training are needed. All stakeholders, including regulators, are responsible for effective communication of the benefit-risk of a vaccine and need to be vigilant about the information communicated to the public. When the regulator shares the public assessment report, the way uncertainty is conveyed is critical; uncertainty exists but also evolves through development.

Anti-microbial resistance (AMR)

AMR represents a major challenge and continues to be a global public health issue. Vaccination is recognised to be a cost-effective tool and developing a vaccine that addresses AMR is a priority. Policies and incentives are needed to make sure that AMR is a focus for developers and included in national immunisation programmes. Addressing the AMR challenge requires a cohesive action-oriented strategy (see slide below).



Future vaccine development – mRNA perspective

Dr Charbel Haber, SVP, Head of Global Regulatory Science, Moderna, USA

Advantages of mRNA technology

With mRNA, the sequence can be modulated, the composition of the lipid nanoparticle can be changed, and the route of administration can be altered to target different tissues. After the mRNA is translated by the ribosome, different antigens can be expressed; some are transmembrane, systemic, secreted extracellularly or intracellular, depending on the application. There is an inherent safety feature of the technology, as the mRNA does not go into the nucleus. Therefore, there are no interactions or interference with the genome DNA.

mRNA technology has broad applicability including the ability to include complex antigens. If the mechanism of action is understood, once the proof of concept is validated, the probability of technical success is much higher than for traditional approaches.

Personalised cancer vaccines

Machine learning is being used to predict the neoantigen peptides that may be the best match for specific tumour epitopes. The sequence is developed and manufactured for each individual patient's tumour. The safety profile of the Individualised Neoantigen Therapy (INT) is similar to the COVID-19 vaccine.

In the rare metabolic disease space, the mRNA technology has the potential to replace enzymes or to create new enzymes.

Regulatory framework

The only published regulatory guidance available for mRNA development is the WHO Guideline for Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations.

The Moderna mRNA technology was selected for the FDA START pilot for rare diseases, which has provided additional support in terms of meetings, communications and guidance on the clinical programmes.

There are some regulatory complexities in terms of how mRNA products are classified and reviewed. If mRNA is used as a vaccine, in the US it is reviewed by the Office of Vaccine Review and Research (OVVR) within CBER, but if the indication is oncology or rare diseases, it is reviewed by the Office of Therapeutic Research (OTP). In Europe, if the mRNA is a vaccine, the product is not considered an advanced therapy medicinal product (ATMP) or gene therapy medicinal product (GTMB). However, when used as a therapeutic mRNA, it is classified as gene therapy (EMA Reflection paper on classification of ATMPs). There is a need for harmonisation on how mRNA medical products are regulated (see slide below).

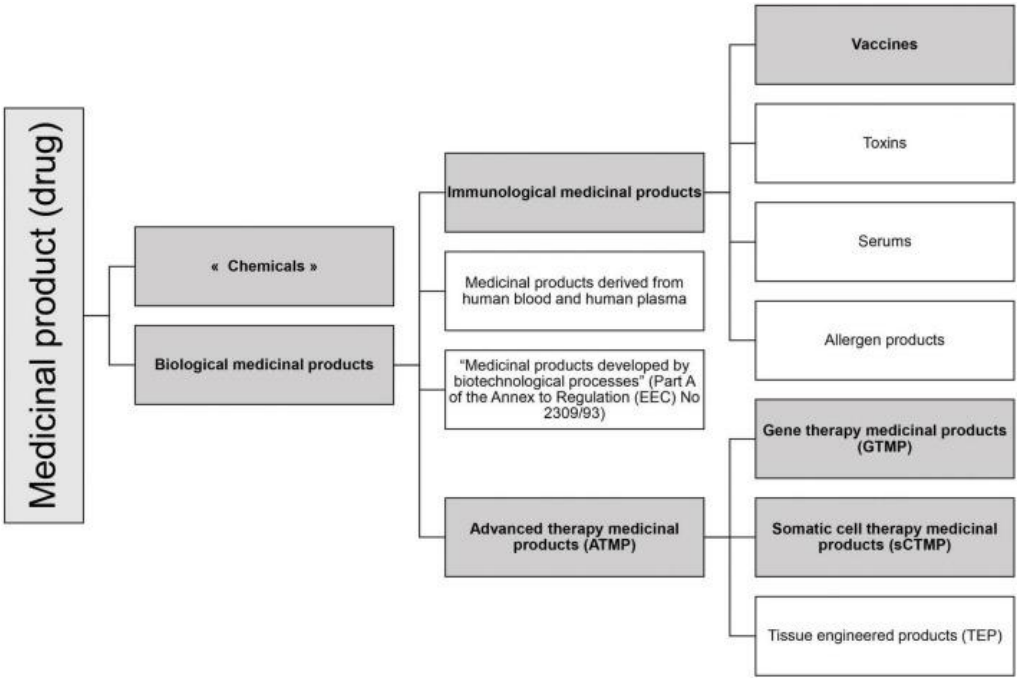
Need for harmonization how mRNA medicines are regulated

- No Regulatory Guidance is available for mRNA Development with the exception of the WHO Guideline for mRNA-based Vaccines:
  - *Evaluation of the quality, safety and efficacy of RNAbased prophylactic vaccines for infectious diseases: regulatory considerations*

- **US-FDA**
  - mRNA Vaccines are reviewed by the Office of Vaccine Review and Research (OVRR) in CBER
  - mRNA Therapeutics are reviewed by the Office of Therapeutics Products (OTP) under CBER

- **EMA**
  - mRNA Vaccines are reviewed as Vaccines and are not considered ATMP/GTMP.
- Reflection paper on classification of ATMPs Rev.1 (08/06/2015) (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf).

  - mRNA Therapeutics are reviewed as GTMP under Biologicals



Medicinal product statuses according to EU legislation. In grey are represented the statuses in which RNA-based drugs can be categorised. Taken from Guerriaud and Kohli (2022).

Manufacturing

There are some nuances in the manufacturing process of mRNA products that impact how they are regulated. The starting material is a circular plasma DNA which is linearised, mixed with polymerase and nucleotides to generate the mRNA and then formulated with lipid nanoparticles to form the final product. The only component of the process related to a biological system is the circular plasma DNA because it is made in E. coli. However, there are manufacturing advances allowing the use of cell-free DNA, which means the whole process becomes synthetic. This is why there is discussion on what type of regulatory framework to use - the vaccine framework, small molecule framework or the biologics framework.

In terms of the platform technology approach, the publication of FDA draft guidance is helpful and could help to harmonise the approach globally. Validation data showing that the manufacturing process is agnostic to the sequence is available, supporting scale up and changes in sequence without changing the manufacturing process. Some regulators view the mRNA itself as the drug substance and some view the combined mRNA and lipid as drug substance, so harmonisation is needed, as this has implication on how regulatory submission dossiers are compiled.

Panel discussion

Each panellist was asked to provide their reflections on future vaccine technologies and their deployment.

Phyllis Arthur, EVP & Head, Healthcare Policy and Programs, Biotechnology Innovation Organization (BIO), USA

- We need to think through the additional regulatory and market access considerations for combination vaccines.
- The platform approach is exciting, and it is great that conversations are happening between regulators to understand how this should be implemented into the regulatory frameworks. Developers are looking to understand how this could shorten drug development timelines when moving from one virus to another.
- The multiple applicability of new technologies will impact traditional development and business models. Different review and reimbursement apply for different use cases.
- What does this mean for investment in infectious diseases? Does it become less attractive because of the ROI? This could have long-term implications.

Dr Matthew Daley, Senior Investigator, Kaiser Permanente Colorado, USA

- To operationalise a new preventative vaccine recommendation, Kaiser has a roadmap developed from other vaccines.
- Budgets are set 18 months in advance and so when a new vaccine is developed, it is not in the pharmacy budget. That is a barrier or constraint for every new vaccine.
- A specific vaccine code has to be assigned, linking it to a code in the electronic health records. The code is used for ordering, clinical decision support and recoding on the immunisation certificate. Until the code is assigned, the vaccine cannot be shipped into the warehouse. Providers will not initiate steps for vaccine coverage until they have the physical vaccine in the warehouse.
- How quickly can we vaccinate our population and how can we achieve the highest coverage? When recommendations coming from NITAGs are clear and unambiguous, then the operationalisation is clear and straightforward. Vaccines recommended for an entire population are more straight forward to implement than recommendations for shared clinical decision making.
- Medical assistants and licensed practical nurses in the US have the authority to give vaccines under 'standing order.' They can do that with a 'should' recommendation, but it is not within their professional authority to do that with a 'may' recommendation.

Prof Lotte Steuten, Deputy Chief Executive, Office of Health Economics (OHE), UK

- HTA bodies have struggled with how to do value assessment on products that are potentially curative because of their high upfront cost and long term yet potentially uncertain benefits. Similar struggles are now seen with vaccine assessment. A full pipeline of high-potential products challenges how to view value and who should be paying for what.
- Iterative HTA is critical. There is never perfect information at the time of HTA decisions and with vaccines, their value crucially depends on their uptake in the real world. Ongoing iterative evaluation that allows for updating the value-based price over time is important.
- Coverage with evidence development already exist for other therapies that have great potential but uncertain long-term benefits.
- Cost-effectiveness estimates based on such uncertain evidence at the time of initial HTA is not necessarily overestimating their value; in fact, results from a coverage with evidence development programme in the UK (the Cancer Drugs Fund) showed that, on average, the estimated cost-effectiveness of therapies was higher *after* additional evidence had been collected, than before.

Richard Hughes IV, Partner, Epstein Becker & Green PC, USA

- Good evidence of the public health problem is needed for prophylactic vaccines that address an unmet need for a low-prevalence serious disease. Raising patient and provider awareness is extremely important for these types of vaccines.
- Recommendations should be clear and implementable, and economics should not get in the way of equity when it comes to recommendations, especially for hard-to-reach subpopulations.
- There is a difference between a prophylactic and a therapeutic vaccine, but that does not mean a therapeutic vaccine is not a vaccine. There are also other preventive modalities that are not vaccines. The lack of clear and consistent terminology creates a lot of confusion for the general public and also for regulators and NITAGs. Ultimately this is a barrier for access.
- Therapeutic vaccines are likely to follow a drug pathway. For example, cancer vaccines designed for individual treatment. Identifying eligible patients and getting them vaccinated is going to need a very thoughtful approach.
- It is also important to think about how other prevention strategies sit alongside vaccines in this spectrum of disease prevention overall.

Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting.

Regulatory agencies		
Dr Claus Bolte	Chief Medical Officer	**Swissmedic**
Dr Agnes Chan	Director, Therapeutic Products Branch	**Health Sciences Authority, Singapore**
Dr Peter Marks	Director	**Center for Biologics Evaluation and Research (CBER), FDA, USA**
Dr Fabrício Carneiro de Oliveira	General Manager (Head Office) of Biological and ATMP	**ANVISA, Brazil**
Dr Supriya Sharma	Chief Medical Advisor	**Health Canada**
Karen Reynolds	Director General, Pharmaceutical Drugs Directorate	**Health Canada**
Sophie Sommerer	Director General, Biologics and Radiopharmaceuticals Drugs Directorate (BRDD),	**Health Canada**
Dr Eveline Trachsel	Head of Medicinal Product Authorisation and Vigilance	**Swissmedic**
HTA agencies, payers and Departments of Health		
Dr Shelley Deeks	Deputy Chief Medical Officer of Health	**Department of Health and Wellness, Nova Scotia, Canada**
Prof Hans-Georg Eichler	Consulting Physician	**Association of Austrian Social Insurance Institutions**
Dr Jaime Pérez-Martín	Head Prevention Service	**Murcia Health Department, Spain**
Dr Detlev Parow	Former Head, Department of Medicines, Medical Remedies and Selective Contracts	**DAK – Gesundheit, Germany**
Academic and non-profit organisations		
Dr June Cha	Policy Director	**Milken Institute, FasterCures, USA**
Prof Eve Dubé	Professor, Department of Anthropology	**Laval University, Canada**
Dr Emily Erbelding	Director, Division of Microbiology and Infectious Diseases	**National Institute of Allergy and Infectious Diseases (NIAID), USA**
Dr Rita Helfand	Senior Advisor for Science, National Center for Emerging and Zoonotic Infectious Diseases	**Centers for Disease Control and Prevention (CDC), USA**
Dr Robert Johnson	Director, Medical Countermeasures program	**Biomedical Advanced R&D Authority (BARDA), USA**
Prof John Lim	Executive Director and Senior Advisor	**Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Ministry of Health, Singapore**

Dr Murray Lumpkin	Deputy Director – Regulatory Affairs / Lead for Global Regulatory Systems Initiatives	**Bill and Melinda Gates Foundation, USA**
Prof Mamoru Narukawa	Professor, Laboratory of Pharmaceutical Medicine	**Kitasato University Graduate School of Pharmaceutical Sciences, Japan**
Dr Peter Neumann	Director, Centre for Evaluation of Value and Risk in Health	**Tufts Medical Center, USA**
Dr Gowri Raman	Associate Director, New Technology, Engagement	**Patient-Centered Outcomes Research Institute (PCORI), USA**
Prof John Skerritt	Enterprise Professor for Health Research Impact	**University of Melbourne, Australia**
Prof Lotte Steuten	Deputy Chief Executive	**Office of Health Economics, UK**
Dr Melinda Wharton	Executive Secretary, Advisory Committee on Immunization Practices	**Centers for Disease Control and Prevention (CDC), USA**
Pharmaceutical companies and consultancies		
Asim Abdul	Senior Director, Global Regulatory Affairs	**GlaxoSmithKline, USA**
Emily Acker	Director, Infectious Disease Policy	**Biotechnology Innovation Organization (BIO), USA**
Silvia Aiolli	GRA Therapeutic Area Head mRNA Vaccines	**Sanofi, Italy**
Dr Phyllis Arthur	Executive Vice President & Head, Healthcare Policy and Programs	**Biotechnology Innovation Organization (BIO), USA**
Ginny Beakes-Read	Head of Global Regulatory Policy	**Johnson & Johnson, USA**
Saiza Elayda	Associate Director, Global Regulatory Policy	**Merck, USA**
Andrew Emmett	FDA Liaison / Executive Director for US Regulatory Policy & Global Intelligence	**Pfizer, USA**
Christine Farquharson	Director, Federal Policy and Government Affairs	**CSL Seqirus, USA**
Dr Jeffery Fu	Chief Business Officer	**Codagenix Inc**
Andrea Gwyn	Vice President, US Vaccines Therapeutic Group, Global Regulatory Affairs	**GlaxoSmithKline, USA**
Dr Charbel Haber	Senior Vice President, Head of Global Regulatory Science	**Moderna, USA**
Richard Hughes IV	Partner	**Epstein Becker & Green PC, USA**
Joseph Kelly	VP, Global Pricing and Market Access Head, Vaccines	**GlaxoSmithKline, USA**

Dr Gennadiy Koev	Vice President, Head of Regulatory Affairs	**Gritstone Bio, USA**
Rebecca Lipsitz	Regulatory Intelligence & Policy, Vaccines & Immune Therapies	**AstraZeneca, USA**
Dr Jacqueline Miller	Senior Vice President and Head, Development, Infectious Diseases	**Moderna, USA**
Shola Oyewole	Chief Innovation Officer	**United Therapeutics Corp, USA**
Eddie Reilly	Chief Regulatory Officer	**Sanofi, France**
Camille Reygrobellet	Vaccines Global Market Access Head	**Sanofi, France**
Craig Roberts	Vice President, CORE Vaccines	**Merck & Co, USA**
Dr David Schmickel	Director Global Regulatory Science Policy and Intelligence, Vaccine Lead	**CSL, USA**
Michael Stirr	AVP and US Region Expert Global Regulatory Affairs	**Sanofi, USA**
Kumaran Vadivelu	Vice President, Vaccines Development	**GlaxoSmithKline, USA**
Pascale Vintézou	Vice President, Global Regulatory Affairs, Vaccines GBU Head	**Sanofi, France**
Centre for Innovation and Regulatory Science (CIRS)		
Dr Magda Bujar	Senior Manager, Regulatory Programme and Strategic Partnerships	**CIRS**
Gill Hepton	Administrator	**CIRS**
Adem Kermad	Senior Research Analyst	**CIRS**
Juan Lara	Senior Research Analyst	**CIRS**
Anna Somuyiwa	Head	**CIRS**
Prof Stuart Walker	Founder and Senior Advisor	**CIRS**

About CIRS

The Centre for Innovation in Regulatory Science is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes. CIRS provides an international forum for industry, regulators, HTA bodies and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, and grants.

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