WORKSHOP SYNOPSIS

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

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

Background

Over the last four years there has been much greater attention paid by industry, regulators, HTA (health technology assessment) 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 BARDA (Biomedical Advanced R&D Authority) in the US, from philanthropic organisations such as the Bill and Melinda Gates Foundation or global coalitions such as CEPI (Coalition for Epidemic Preparedness Innovations), 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 NITAGs (National Immunisation Technical Advisory Groups) 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 sessions

This multi-stakeholder workshop consisted of a series of sessions (see programme) featuring presentations and panel discussions, as well as three parallel breakout discussions. The breakout groups were asked to discuss and develop recommendations on three topics:

- What collaborative evaluation models and metrics should be developed to support vaccine regulatory or funded access?
- How do we evolve the regulatory system to accommodate new vaccine technologies and challenges?
- How can we ensure that vaccine health economic assessment/HTA is fit for the future?

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 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 OHE (Office of Health Economics) 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 mis 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 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.

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Recommendations from breakout 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 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 RWE (real-world evidence) 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.

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.

Workshop Programme

Session 1: The changing vaccine landscape	Session 2: De-risking vaccine development
Chair: Dr Supriya Sharma, Chief Medical Adviser, Health Canada	
Dr Emily Erbelding, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), USA	**Kumaran Vadivelu,** Head, Vaccines Development, GlaxoSmithKline, USA
Prof John Skerritt, Enterprise Professor for Health Research Impact, University of Melbourne, Australia	**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, BIO (Biotechnology Innovation Organization), USA
Dr Peter Marks, Director, Center for Biologics Evaluation and Research, 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, PCORI, USA **Richard Hughes IV,** Partner, Epstein Becker & Green PC, USA	
Session 3: Regulatory challenges and metrics	**Session 4: Are current health technology and NITAG assessment models for vaccines fit for purpose?**
Chair: Prof Hans-Georg Eichler, Consulting Physician of the Association of Austrian Social Insurance Institutions	
Dr Fabrício Carneiro de Oliveira, General Manager (Head Office) of Biological and ATMP, ANVISA, Brazil	**Prof Lotte Steuten,** Deputy Chief Executive, Office of Health Economics (OHE), UK
Dr Rita Helfand, Senior Advisor for Science, National Center for Emerging and Zoonotic Infectious Diseases, Center for Disease Control and Prevention, USA	**Peter Neumann,** Centre for Evaluation of Value and Risk in Health, Institute of Clinical Research and Health Policy Studies, Tufts University, USA **Craig Roberts,** VP, Outcomes Research, Merck, USA **Dr Melinda Wharton,** Executive Secretary. Advisory Committee on Immunization Practices Centers for Disease Control and Prevention, USA **Dr Jaime Pérez-Martín,** Head Prevention Service, Murcia Health Department, Spain
Andrew Emmett, FDA Liaison / Executive Director for US Regulatory Policy & Global Intelligence Pfizer, USA	
Dr Claus Bolte, Chief Medical Officer, Swissmedic	
Session 5: Breakout discussions - Priority research areas and how to address policy challenges	**Session 6: Future vaccine technologies and depolyment**
Chair: Prof John Skerritt, Enterprise Professor for Health Research Impact, University of Melbourne, Australia	**Chair: Dr Claus Bolte,** Chief Medical Officer, Swissmedic
Breakout 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	**Pascale Vintézou,** Vice President, Vaccines GBU Head, Sanofi, France
Breakout 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	**Dr Charbel Haber,** SVP, Head of Global Regulatory Science, Moderna, USA
Breakout 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	**Richard Hughes IV,** Partner, Epstein Becker & Green PC, USA **Dr Matthew Daley,** Senior Investigator, Kaiser Permanente Colorado, USA **Phyllis Arthur,** EVP & Head, Healthcare Policy and Programs, BIO, USA

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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