WHITE PAPER

Vaccine Market Access in 100 Days: From Pipe Dream to Reality

Samantha James
Associate Director, Market Access Communications

Ruth Chapman
Senior Research Scientist, Modeling and Simulation

Anna D'Ausilio
Director, Value and Access Consulting

Sarah Rosen
Senior Director, Project Management, Non-Interventional Studies

Ariel Berger
Executive Director, Integrated Solutions, Real-World Evidence

Matt Quaife
Senior Research Scientist, Patient-Centered Research

Authors are affiliated with Evidera, part of the PPD clinical research business of Thermo Fisher Scientific

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Contributors are affiliated with Evidera, part of the PPD clinical research business of Thermo Fisher Scientific

Preventive vaccines have played a crucial role in protecting people around the world from serious and often deadly infectious diseases, particularly during pandemics. Despite their importance, the average timeline for vaccine development stretches from 10 to 15 years.[1,2] Adding to these delays, the market access process can dramatically prolong the time to market compared with other pharmaceuticals, partly due to complex and opaque pathways.[3] There is a clear need for a strong strategy and implementation plan centered around preparation, innovation, and collaboration to benefit global populations, societies, industries, and economies by minimizing the direct and indirect burden of vaccine-preventable disease. To support our manufacturing partners and expedite patient access to vital disease prevention, Evidera, part of the PPD™ clinical research business of Thermo Fisher Scientific, has launched a new "100 days to vaccine market access" initiative to recognize hurdles and propose solutions for expediting patient access to vaccines.

1. Why is Vaccine Market Access so Challenging?

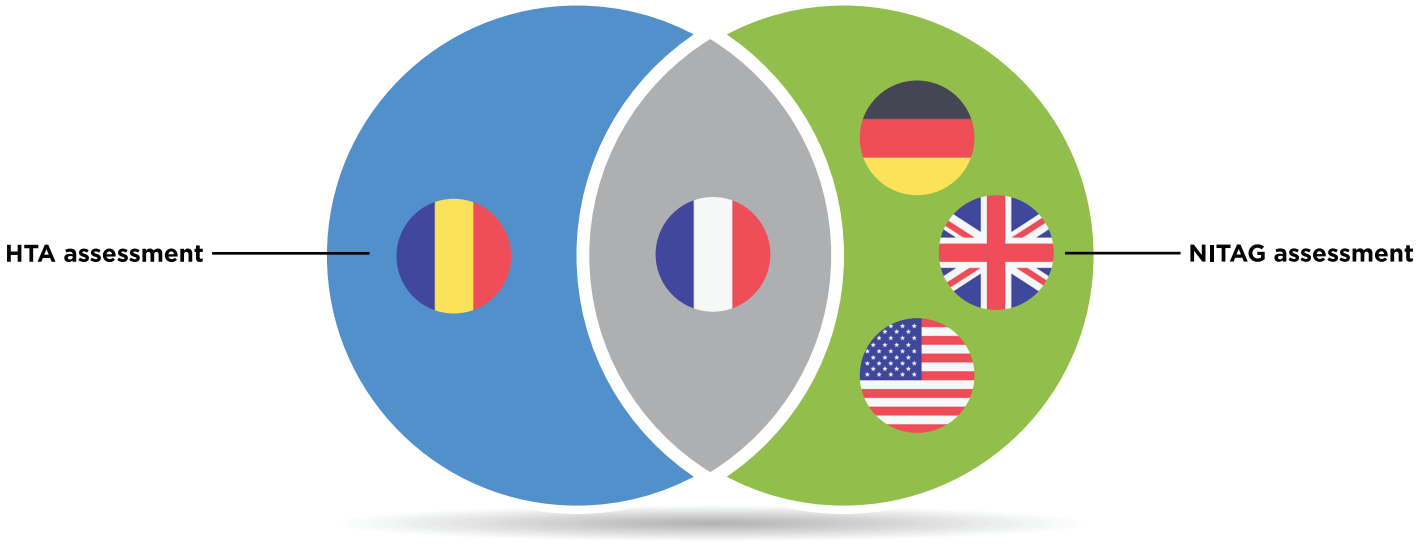
Vaccine market access pathways differ significantly from other pharmaceuticals due to National Immunization Technical Advisory Group (NITAG) involvement. NITAGs are multidisciplinary advisory groups tasked with conducting independent and evidence-based assessments of vaccines and immunization strategies.[3] Most countries in Europe and North America have a NITAG, with only four countries (Hungary, Romania, Cyprus, and Kosovo) relying on health technology assessment (HTA)[a,4] or other mechanisms to establish vaccine market access.[5]

Understanding the current landscape of vaccine market access is extremely important for any biopharmaceutical company considering or undertaking vaccine development. Recognizing and understanding the differences across markets and potential hurdles better positions manufacturers to address these challenges early in their strategic planning. These challenges vary geographically; while this white paper focuses mostly on high-income and high-middle-income countries, the need to better understand the situation in lower and lower-middle income countries should not be overlooked.[6]

Influence and Impact of NITAGs on the Assessment of Vaccines

The role of NITAGs and HTA agencies in decision-making for vaccines differs by country, with various evidence requirements and multiple stakeholders involved (Figure 1). NITAG decisions are often credited with being the most influential drivers of vaccine market access; however, NITAGs have unique challenges that may complicate and delay decision-making.

Figure 1. Vaccine market access may be the responsibility of a NITAG (as in Germany, England, and the US), an HTA (as in Romania), or both (as in France)



HTA = health technology assessment; NITAG = National Immunization Technical Advisory Group

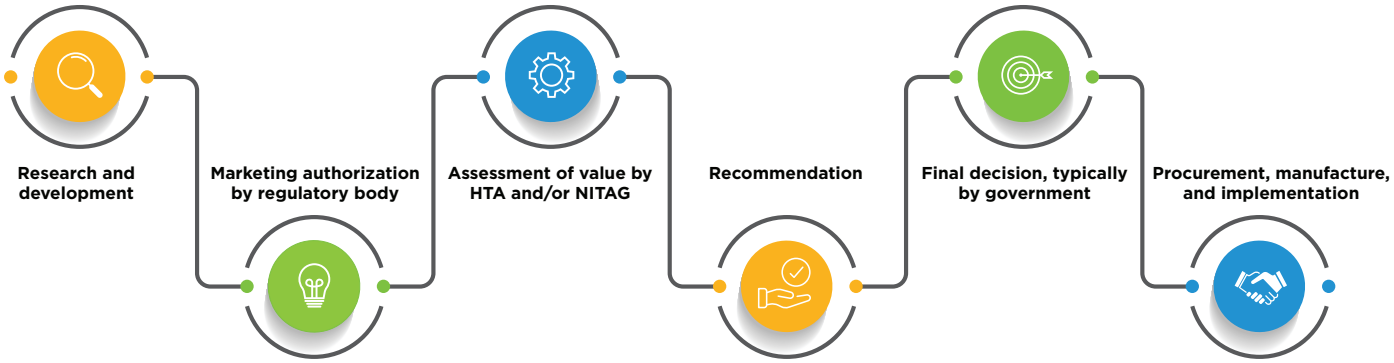
NITAGs play a crucial role in providing guidance to decision-makers regarding the selection of recommended vaccines, appropriate administration schedules, the target population for vaccination, and reimbursement policy. Recommendations made by NITAGs to decision-makers are non-binding in most countries (the UK being an exception), but are typically implemented, emphasizing the influence and importance of NITAGs in vaccine decision-making.[7] Vaccine developers must plan for key differences in evaluation and decision-making factors of NITAGs vs. HTA bodies to facilitate timely vaccine market access.

a. While NITAGs focus on providing recommendations and guidance on immunisation strategies and policies, HTA is conducted to inform adoption, reimbursement, and utilisation of healthcare technologies (including medical devices, pharmaceuticals, procedures, and interventions) based on a systematic evaluation of their clinical, humanistic, economic, and societal impact.

Complex and Poorly Transparent Decision-making Processes

At first glance, vaccine market access processes appear straightforward, typically passing from market authorization through HTA and/or NITAG evaluation to a recommendation that ultimately leads to a government decision to reimburse and/or procure the vaccine (Figure 2). However, the reality is more complicated, with often-cited obstacles to achieving market access including issues related to clinical data (e.g., lack of effectiveness data or safety issues), economic factors, process clarity, vaccine implementation, and patient education and vaccine awareness (Figure 3).[3] Many of these factors are beyond the remit of NITAGs, being intrinsic to the vaccine itself (e.g., long-term evidence of effectiveness and/or safety in the target population) and/or related to complex country-level factors, including but not limited to budget availability. Nevertheless, there is a substantial opportunity for improvement in NITAG processes, most notably in ensuring clarity and precision in the criteria and requirements for initiation, prioritization and evaluation of NITAG submissions. This can be reasonably expected, given that many NITAGs remain in their infancy, having been established within the last 10 years. NITAG processes can and will become clearer with time and investment, particularly given the support of organizations such as the World Health Organization (WHO) and the Robert Koch Institute.[6] In the meantime, vaccine manufacturers must anticipate these challenges to help avoid delays in vaccine market access.

Figure 2. Flowchart illustrating the typical vaccine market access process in Europe and North America (adapted from Laigle, 2021[3])



HTA = health technology assessment; NITAG = National Immunization Technical Advisory Group

Figure 3. Barriers to timely vaccine market access (adapted from Laigle, 2021[3])

Timelines are Significantly Longer for Vaccines than Other Pharmaceuticals

Except for the COVID-19 vaccines, the time between market authorization and HTA/NITAG recommendation is longer for vaccines compared with other pharmaceuticals. In Europe, for example, the duration between market authorization and a NITAG decision for three vaccines (pneumococcal, human papillomavirus, and quadrivalent influenza) exceeded six years in almost 50% of the 28 countries studied. Only four countries (13%) reported a timeline of fewer than two years for this process.[3] The median time frame between market authorization and HTA outcome for other pharmaceuticals was measured in days rather than years, and rarely exceeded 12 months in studies conducted in Australia, Canada, and several European countries (Table 1). This generalization also applies for oncology and orphan drugs, which are hypothesized to require longer assessment period.[8,9] There is limited published evidence in the US; we are undertaking a study to address this evidence gap.

Table 1. Time between market authorization and NITAG (vaccines) or HTA (other pharmaceuticals) advice

Author, year	Study date	Pharmaceutical(s) included	Country(ies)	Median time between MA to NITAG or HTA advice	
VACCINES					
Laigle, 2021[3]	2018 to 2019	Pneumococcal, human papilloma virus and quadrivalent influenza vaccine	28 countries across Europe	>6 years in 13 countries (46%) 2-6 years in 11 countries (39%) <2 years in 4 countries (15%)	
OTHER PHARMACEUTICALS					
Wang, 2020[9]	2014 to 2018	HTA approved drugs (n=169), with sub-analyses conducted for oncology drugs and new active substances		**MA to HTA submission:**	**HTA submission to advice:**
			Australia	-107 days[a]	125 days
			Canada	-30 days[a]	216 days
			UK (NICE)	7 days	266 days
			Italy	23 days	374 days
			France	29 days	157 days
			Germany	42 days	170 days
			Spain	49 days	221 days
Connolly, 2019[8]	2015 to 2017	RR (n=158) and standard HTAs (n=49), with sub-analyses conducted for oncology and orphan drugs		**MA to HTA submission:**	**HTA submission to advice:**
			Ireland	MA to RR submission:	59 days
				RR appraisal:	32 days
				RR decision to HTA submission:	115 days
				HTA appraisal:	131 days
				Company response:	42 days
Maervoet, 2012[10]	2006 to 2011	Innovative drugs granted EMA approval (n=111)	Belgium	348 days	
			France	279 days	
			UK (NICE)	399 days	

a. HTA submissions can be made prior to market authorization in Australia and Canada
HTA = health technology assessment; MA = marketing authorization; NICE = National Institute for Health and Care Excellence; NITAG = National Immunization Technical Advisory Group; RR = rapid review; UK = United Kingdom

2. What are the Consequences of Delayed Vaccine Availability?

Delays in vaccine market access can have dramatic consequences on populations, societies, industries, and economies, driven by the direct clinical and economic burden of vaccine-preventable disease, and compounded by lost productivity and other indirect costs. Preventing the burden driven by delayed vaccine market access is critical, particularly given that more than 966 new vaccines are in clinical development in the infectious disease space alone (as of January 2023),[11] with global market potential predicted to grow from 83.98 billion US dollars (USD) in 2024 to USD 139.17 billion by 2032.[12]

The COVID-19 pandemic is a prime example to illustrate the clinical impact of delayed access to a vaccine. Despite accelerated vaccine development and a widespread willingness to vaccinate, there was a substantial lag (up to 4 months) in the time to the first COVID-19 vaccination in low-income countries (LIC), lower-middle-income countries (LMIC), and upper-middle-income countries (UMIC) compared with high-income countries (HIC).[13,14] The consequent impact on clinical outcomes due to this delay is staggering. Between 6% and 50% of COVID-19 deaths in LICs and LMICs could have been prevented if these countries had access to vaccines at the same time as the US, even without increasing overall vaccination rates.[14] Although delays were most likely due to factors beyond market access pathways, such challenges with manufacturing, affordable pricing, and global allocation,[15] insights can be gained regarding the impact of delays in access on clinical and health economic outcomes.

The lag time to the first vaccination is also likely to have had a substantial impact on the number of COVID-19 cases. Every day of delayed access to COVID-19 vaccines vs. HICs was associated with a 1.92%, 1.11% and 3.46% cumulative increase in the number of COVID-19 cases in LICs ($p = 0.0395$), LMICs ($p = 0.2351$), and UMICs ($p = 0.0001$), respectively.[13] The consequent increase in viral transmission would have promoted the emergence of new and potentially more virulent SARS-CoV-2 variants, underlying the public health importance of providing timely access to vaccines.[16]

Health economic outcomes are also impacted by delayed vaccine market access. A study conducted of 27 African countries used a dynamic transmission model to demonstrate that the effectiveness of vaccines on clinical outcomes (including cases, deaths, and disability-adjusted life years) worsened with each month that vaccination deployment was delayed throughout 2021.[b, 17] It found delayed vaccine deployment was associated with higher incremental cost-effectiveness ratios (i.e., lower cost-effectiveness) than earlier deployment.

b. Vaccines must be able to be manufactured at scale (e.g., via technology transfer), priced affordably and allocated globally to facilitate equitable market access globally. These challenges are beyond the scope of this paper, but are well documented in a Health Policy paper authored by Wouters, OJ, et al. 2021[15]

3. Is it Possible to Accelerate Vaccine Market Access?

The COVID-19 Paradigm Shift

COVID-19 prompted an overhaul in the development and deployment of vaccines. Vaccine research and development was accelerated from 10 years to less than 1 year,[2] enabled by[18]:

- Use of flexible clinical trial designs (e.g., overlapping, parallel, or combined phase trials)
- Timely advances in innovative development and manufacturing platforms (including messenger RNA technology)
- Global collaboration between the scientific community, governments, and international organizations
- Substantial public funding to cover the costs of vaccine research and development

Regulatory vaccine approval processes were also overhauled. In Europe and the US, for example, this was facilitated by the creation of dedicated COVID-19 task forces, the introduction of "rolling" regulatory reviews, the use of accelerated marketing authorization pathways (conditional marketing authorization in Europe and emergency use authorization in the US),[18] and massive public health awareness programs. The routine NITAG assessment process was often side-stepped throughout the COVID-19 pandemic. Instead, NITAGs were often tasked with issuing vaccine guidance on topics such as off-label use, prioritization, and scheduling. The combined success of these innovations resulted in 2.8 billion doses of COVID-19 vaccines being delivered within 16 months of the first clinical trial,[19] raising hopes for innovation and acceleration in other therapeutic areas.[20]

New Initiatives to Expedite Vaccine Development, Distribution, and Market Access

The global response to COVID-19 included an unprecedented acceleration in the time from "lab to jab," touching all aspects of vaccine research, development, regulatory approval, manufacture, and access. Many new initiatives are now in place across the development and access pathways. Examples of notable initiatives focused on accelerating patient access to vaccines include:

- The Coalition for Epidemic Preparedness Innovations (CEPI) "100-day mission," which aims to develop a safe and effective vaccine within 100 days of the sequencing of a new pathogen[2,21]
- The International Pandemic Preparedness Secretariat (IPPS), which is an independent entity tasked with coordinating member states, the private sector and global health institutions to ensure global progress toward the 100-day mission[22]
- The Center for Global Development's "second 100 days" mission, which advocates for a coordinated strategy to assure speedy and equitable manufacturing and procurement of medical countermeasures (including vaccines) in the wake of a pandemic risk[23]
- Multiple initiatives from Vaccines Europe, an industry-led coalition focusing on improving market and patient access to vaccines, including by advocating for harmonization of vaccine market access assessment and decision-making in Europe[24,25]

100-day Mission Mpox Clock

On August 14, 2024, the International Pandemic Preparedness Secretariat (IPPS) launched the 100-day mission clock for Mpox after it was declared a public health emergency of international concern by the WHO. At the onset, three Mpox vaccines had been authorized; however, none were approved for use across all affected countries. The aim of the 100-day mission in this case was to ensure timely vaccine approval, availability, and delivery.[26] As of day 43 (September 26, 2024), less than 3% (265,460) of the 10 million doses required[27] had been delivered to the Democratic Republic of Congo, where vaccines are most urgently needed. As of October 31, 2024, the vaccine had yet to be rolled out to patients.[28,29]

IPPS will continue to track progress toward the 100-day mission, along with progress toward the "second 100 days," which will focus on accelerating manufacturing and roll-out. Evidera will monitor the 100-day mission's progress to pinpoint opportunities where our expertise could expedite vaccine market access processes for this and future public health emergencies.

4. Evidera's "100 Days to Vaccine Market Access" Initiative: How can We Achieve Vaccine Market Access within 100 Days of Marketing Authorization?

In recognition of the critical need to accelerate the time to market for vaccines, we have launched an initiative to develop a comprehensive global NITAG submission package within 100 days of market authorization. This initiative consists of leveraging published evidence and our expertise and experience in NITAG/HTA processes and requirements to accomplish the following:

- Map the current process for developing global NITAG submission
- Identify key barriers to developing a NITAG/HTA submission pack within 100 days of regulatory approval
- Develop an overarching strategy to help vaccine manufacturers accelerate their vaccine market access timelines
- Illustrate how this strategy can be used to achieve vaccine market access within 100 days of market authorization

Mapping the Current Process

The typical process for the development of a NITAG/HTA submission package begins with the formulation of a launch strategy and an evidence generation plan (Figure 4). The launch strategy and the evidence generation plan would ideally be informed by a diverse group of experts from various disciplines such as market access, health economics and outcomes research (HEOR), medical affairs, regulatory affairs, patient advocacy, and health policy/government affairs. This collaborative approach ensures alignment, expediency and efficiency across functions.

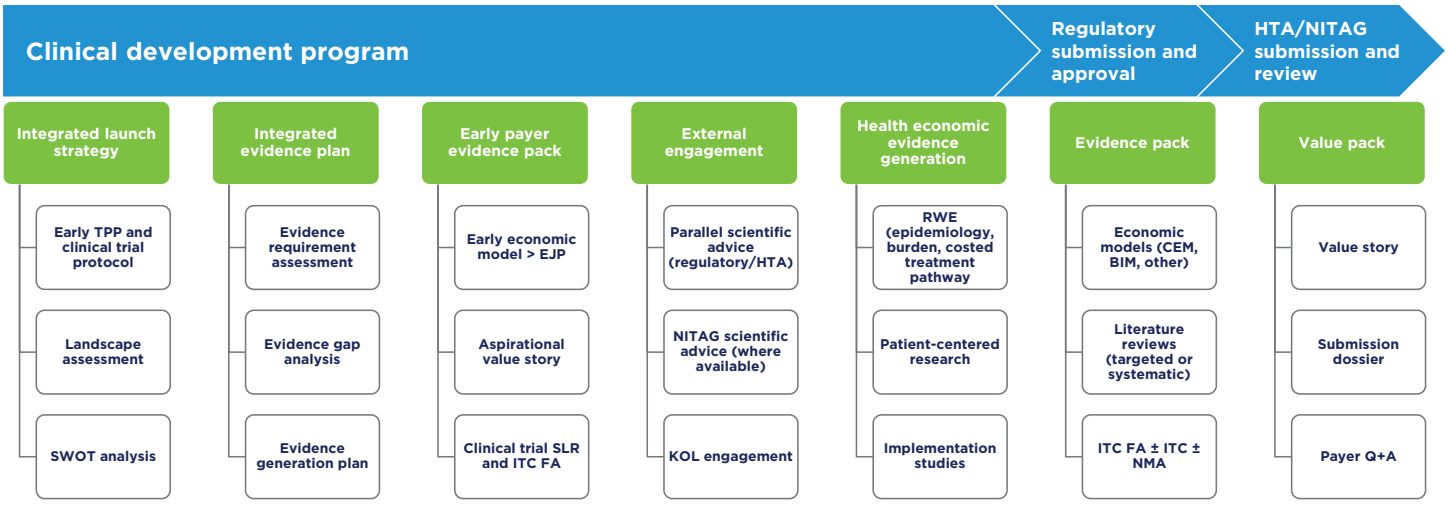
During the early stages of clinical trial development, seeking external scientific advice from HTAs and/or NITAGs (or scientific experts if formal scientific advice is not available) is crucial. This advice primarily focuses on evaluating the clinical trial design, the evidence generation plan, and the early economic model. The input from external scientific advisors helps to refine and optimize these aspects of the trial.

Health economic evidence generation (hereon called "evidence generation") begins as early as possible during the clinical development of the vaccine and may involve conducting real-world evidence (RWE) studies and patient-centered research. Development of the NITAG/HTA submission pack follows, typically commencing during the phase 3 clinical trial. This pack includes essential elements, such as the value narrative, dossier, economic models, literature reviews, and indirect treatment comparisons (ITCs), that are continuously updated as the situation, strategy, and evidence base evolve. Some NITAGs/HTAs may additionally require specific elements, such as systematic literature reviews on specific topics, to be completed within six months of submission.

Once licensure is obtained for the vaccine, the evidence and value packs are finalized as quickly as possible. In some cases, adapting global materials may be necessary to meet the specific requirements of local NITAGs/HTAs and other decision-making bodies. During the review process, manufacturers may be required to engage with the NITAG/HTA to address any uncertainties or provide additional clarification. These interactions are crucial for the decision-making process.

The time required to develop a NITAG/HTA submission pack can vary significantly, depending on multiple factors such as the clinical development program, evidence generation plan, and perceived urgency. This process can extend over multiple years, especially when RWE generation is necessary.

Figure 4. Simplified outline of the typical process for the development of a NITAG/HTA submission package



BIM = budget impact model; CEM = cost-effectiveness model; EJP = economically justifiable price; FA = feasibility assessment; HTA = health technology assessment; ITC = indirect treatment comparison; KOL = key opinion leader; NITAG = National Immunization Technical Advisory Group; NMA = network meta-analysis; RWE = real-world evidence; SLR = systematic literature review; SWOT = strengths, weaknesses, opportunities and threats; TPP = target product profile

Identifying the Barriers

We have conducted a multidisciplinary analysis based on published evidence and our collective expertise and experience to identify key barriers that may hinder the development of a NITAG/HTA submission pack within 100 days of market authorization. These barriers include:

- Lack of clarity, alignment, and efficiency in key areas, including overall strategy, development and evidence plan, and stakeholder responsibilities, across the many internal and external stakeholders involved in the preparation of a NITAG/HTA submission
- NITAG processes and requirements may be unclear or lack transparency
- Evidence generation is time-consuming
- Gaps and uncertainties in the evidence base may delay submission and review

Evidera's Three-pillar Strategy

To address these challenges, we have identified a range of potential solutions, revolving around three key pillars: prepare, innovate, and collaborate (Table 2).

Table 2. Solutions for developing a NITAG/HTA submission pack within 100 days of regulatory approval

BARRIER	SOLUTION		
	PREPARE	INNOVATE	COLLABORATE
Strategy, plan and/or responsibilities may be unclear and/or inefficient	• Develop a detailed 100-day roadmap, including strategy, checklists, timelines and responsibilities, minimizing duplication of efforts and streamlining review processes	• Leverage multidisciplinary expertise, experience, and research to identify new opportunities for improvement	• Establish a multidisciplinary team responsible for the 100-day mission • Conduct simulation exercises to identify potential challenges
NITAG processes and requirements are often unclear and poorly transparent	• Leverage shared expertise and experience to ensure familiarity with NITAG/HTA processes and requirements • Maintain a catalogue of NITAG/HTA submission templates and guidance documents	• Seek opportunities to advocate for improvement (e.g., rolling NITAG/HTA review to allow continual submission of new data)	• Cultivate relationships with key decision-makers and other stakeholders • Foster network of key opinion leaders to provide insights and experience • Seek early and integrated scientific advice
Evidence generation is time-consuming	• Maintain a library of pre-approved disease-agnostic materials (e.g., submission templates and protocols) • Ensure early development of an RWE generation plan based on analysis of data and evidence requirements	• Seek innovative approaches to accelerate the generation of clinical and real-world data (e.g., AI-enabled data cleaning, literature review and clinical trial tokenization)	• Align with other stakeholders on the acceptability of methods used to accelerate vaccine development (e.g., proxy outcomes and innovative trial design)
Gaps and uncertainties in evidence base may delay submission and review	• Develop a multidisciplinary checklist to ensure that no evidence requirements are overlooked • Identify potential evidence gaps as early as possible	• Seek innovative ways of generating data, such as using predictive analytics and global surveillance data to predict incidence and rapidly identify high-risk populations	• Seek multidisciplinary expertise and experience to inform integrated evidence generation plan • Seek early and integrated scientific advice

a. Including but not limited to NITAG/HTA bodies, regulators, policymakers, governmental and non-governmental organizations and academia
b. For example, proxy outcomes (e.g., biomarkers, immunobridging and immunogenicity) and innovative trial design (e.g., digital twin studies and adaptative trial design)
AI = artificial intelligence; HTA = health technology assessment; NITAG = National Immunization Technical Advisory Group; RWE = real-world evidence

5. How Can the Three-pillar Strategy be Put into Practice?

There are many opportunities and challenges associated with the launch of new vaccines. Successful planning includes understanding the evidence requirements for various stakeholders, the evolving considerations for approval and market access, and the changing regulations potentially affecting vaccine development. Several critical activities that should be conducted to ensure the development of a robust data package and positive launch environment are RWE, patient-centered evidence, and early scientific advice and stakeholder engagement. Our three-pillar strategy centered around preparation, innovation, and collaboration can be used to guide the development and implementation of vaccine market access strategies.

Real-world Evidence

Regulators and payors are increasingly integrating RWE of safety, effectiveness, and value into their decision-making. However, RWE studies may require many months or years to complete, potentially delaying the submission and/or evaluation of NITAG/HTA submission dossiers.

Prepare: Considering all uses of RWE early in the vaccine development process is extremely beneficial to plan efficient and effective evidence generation strategies that can optimize and expedite vaccine development, approval, and market uptake (Figure 5). This planning will help advise a relevant real-world data strategy for the life cycle of the asset, and early preparation will inform how manufacturers will create the necessary infrastructure and personnel for all relevant RWE generation activities. RWE needs will vary over time; however, manufacturers that invest in evidence generation planning activities will be prepared with a solid RWE strategy, ensuring the appropriate sources are available at the right time to support RWE generation needs.

Figure 5. Potential uses of real-world evidence throughout the vaccine development process

Early in development

- Providing insights to predict disease progression
- Understanding epidemiologic (e.g., incidence, prevalence, risk factors), clinical, and economic burden of illness
- Guiding elements of trial design
- Informing epidemiologic models to predict infection outbreaks to help with clinical trial site selection and subject recruitment
- Informing economic models to illustrate the budget impact and/or cost-effectiveness of vaccination
- Highlighting other anticipated or actualized benefits associated with vaccination

Peri-marketing authorization

- Demonstrate a vaccine's potential benefit versus risk

Post-marketing authorization

- Post-marketing commitments (e.g., to monitor real-world vaccine effectiveness and safety, including pregnancy registries and other post-approval safety studies)
- Expand existing recommendations (see Case Study 1)
- Demonstrate and quantify hypothesized advantages/benefits (see Case Study 1)

Case Study 1: Leveraging Real-world Evidence to Expand Marketing Authorization

Background & Challenge

- The US Advisory Committee on Immunization Practices (ACIP) recommends use of respiratory syncytial virus (RSV) vaccine in certain subpopulations
- Our client asked for our support with:
  - Demonstrating the prevalence of risk factors for severe outcomes of RSV, which would help increase awareness of the importance of vaccination
  - Expanding uptake of RSV vaccine in these subpopulations
  - Broadening ACIP recommendations to include additional subpopulations

Approach

- We conducted an analysis of National Health and Nutrition Examination Survey (NHANES) data to determine:
  - The number and percentage of US adults with ≥1 risk factors for severe RSV infection (overall and by age group)
  - The number and percentage of US adults with various risk factors for severe RSV infection (overall and by age group)
  - The association between various characteristics (e.g., demographics, social determinants of health) and the presence of ≥1 of these risk factors

Impact

This study:

- Demonstrated the degree to which the US population has risk factors that predisposes them to severe outcomes of RSV infection
- Helped identify additional high-risk subpopulations not captured by ACIP recommendations at the time of study initiation, including adults aged 50-59 years, certain ethnic groups, and those of lower socio-economic status
- Was used by the client in their successful advocacy to expand the existing age indication for their RSV vaccine
- Highlighted the need to consider social and economic inequities in the development of RSV vaccination implementation programs

Depending on its formulation and/or administration schedule, additional evidence generation efforts may be required to further demonstrate hypothesized advantages/benefits of a particular vaccine. For example, an asset that combines two vaccines into a single dose is likely to enable more efficient vaccination processes in terms of the time (and cost) required to vaccinate individuals as well as the degree of coverage against disease. To demonstrate these hypothesized benefits, a manufacturer will likely need a multi-pronged approach to evidence generation that, at a minimum, would include:

- RWE generation to illustrate current levels of coverage against each of the two relevant infectious diseases associated with the current standard of care and the requisite burden/cost of these infections.
- Time-driven activity-based costing or similar methodology to demonstrate and contrast the time and cost to pharmacies and clinics, respectively, associated with the use of the combination vaccine vs. the use of the two vaccines currently required to provide the same level of coverage against these infections.
- An economic model that can forecast clinical and healthcare resource and utilization (HCRU) outcomes across a relatively large population over a relatively long period of time.

Innovate: The often-urgent need for vaccines creates an opportunity for innovative trial designs to reach larger populations faster and produce the right evidence for regulatory and payer decisions. An example of such an innovation is provided in Case Study 2.

Case Study 2: Time and Cost Model to Demonstrate Benefits of New Vaccine Technology

Background & Challenge

- Client developing new technology, a pre-filled syringe (PFS), which is expected to reduce errors and minimize overall time and effort to prepare and administer vaccine (vs. reconstitution)
- Evidence of benefit of PFS (vs. reconstituted) to pharmacies and clinics required to demonstrate differentiation
- To achieve this, the client needed to demonstrate differences in time and cost required to prepare and administer PFS vs. reconstituted vaccine; ideally per-vaccination, as well as across a broader population and longer period

Approach

- Cross-functional team executed two integrated workstreams to determine and project time and cost required to vaccinate
- Workstream #1: RWE Generation
  - Using TDABC methods, informed by HCP panel, two process maps were created (one for PFS; one for reconstituted)
  - Detailed process maps demonstrated complete vaccination process, including resources required per step (personnel, equipment, medication, physical space), and estimates of time and cost thereof
  - Used for comparisons of time and cost required to administer PFS vs. reconstituted product
- Workstream #2: Economic Model
  - Developed and implemented a dynamic cost model, leveraging inputs from Workstream #1, to project time and costs required to vaccinate PFS vs. reconstituted to a broader population over a longer time period

Impact

- Client can demonstrate time and cost benefits to pharmacies / clinics of PFS vs. reconstituted
  - Dynamic, tailored cost model projected expected benefits in terms of efficiency, decreased waste, and opportunity cost savings at scale
- Evidence informs argumentation of real-world product value of PFS (vs. reconstituted) and will be used to support launch activities

Abbreviations: HCP = healthcare provider; PFS = progression-free survival; RWE = real-world evidence; TDABC = time-driven activity-based costing

Collaborate: For the best outcomes, vaccine manufacturers will want their plans to be informed by a team of experts in various disciplines, including epidemiology, statistics, real-world data, health economics, market access in the country/countries of interest, patient-centered research, and data science (to leverage existing data or design research to generate new data). Depending on the product and its differentiation from other existing vaccines/assets under development, other disciplines such as policy and government affairs may also need to be consulted.

Patient-centered Evidence

Placing patient perspectives at the heart of an evidence generation strategy can demonstrate vaccine value to recipients and societies, substantiate claims on differentiation and risk-benefit balance, and highlight unmet needs from a patient perspective.

Prepare: Patient-centered research should ideally be incorporated early in the development process to maximize impact on the speed to vaccine approval and access. By understanding patient perspectives from the beginning, many issues faced during vaccine development and approval can be anticipated, minimized and more easily overcome. The use of evidence directly generated from patients can inform several areas of development. Patient-centered evidence can:

- Characterize vaccine-hesitant attitudes, behaviors, and subgroups
- Assess patients' willingness to accept vaccine-associated risks in return for efficacy
- Measure and understand health state utility for vaccine-preventable diseases, to obtain accurate estimates of vaccine avertable burden
- Describe and quantify the value to patients of differentiating aspects such as multi-virus or multi-valency protection or more convenient administration schedules
- Predict the uptake of different vaccine formulations
- Identify specific concerns and barriers to vaccine acceptance or hesitancy, allowing manufacturers to highlight differentiating aspects or generate supplementary evidence to get ahead of potential criticisms

Innovate: Patient-centered research can provide rapid and robust insights to inform market access and HTA discussions. Innovative patient engagement strategies can lead to more patient-centered clinical trials and treatment approaches. Involving patients in the design and execution of clinical trials can yield more relevant and comprehensive data, which can expedite regulatory approval. For example, incorporating patient-reported outcomes can provide a more holistic view of treatment efficacy and safety, making the case for approval more compelling.

Collaborate: By building partnerships with patient advocacy organizations, healthcare providers, and regulatory agencies, companies can ensure that their research addresses the needs and concerns of all stakeholders, identifies and addresses barriers to adoption, and facilitates the development of tailored implementation plans. These partnerships, especially when fostered early in vaccine development, can help manufacturers secure funding for the research (including RWE studies) that will have the greatest impact on approval. A collaborative approach can also build trust and support for new treatments, facilitating smoother market entry. For example, we collaborated with a client to conduct a patient-centered research study to demonstrate the impact of reducing the number of injections on willingness to be vaccinated against meningococcal disease (see Case Study 3). The research also identified and characterized vaccine-hesitant populations across various dimensions, including income and geography, as well as examining differences between adolescents and their parents or guardians. These insights helped inform the market access strategy for the vaccine.

Case Study 3: Eliciting Patient-Centered Evidence on the Value of Multivalent Protection

Background & Challenge

- We worked with a manufacturer in a crowded market for multi-valency invasive meningococcal disease (IMD) vaccines, with similar benefit and risk profiles
- Sponsors are investing in vaccines requiring fewer shots to achieve multi-valent protection, but the value of this to patients is unclear
- Objective: Understand patient preferences for multi-valent vaccines, and characterize differences between adolescent and parent/guardian preferences

Approach

- A patient preference study was conducted among adolescents and parents/caregivers in the US
- A discrete choice experiment elicited the relative importance of vaccine attributes to adolescents and caregivers, explored willingness to be vaccinated, and examined heterogeneity in predicted uptake among population groups

Impact

- Results suggest that multi-valent vaccines are valued by adolescents and caregivers due to reduced dosing requirements
- Increased protection could encourage marginally vaccine hesitant populations to obtain vaccination
- Results informed differentiation and market access strategy

Early Scientific Advice and Stakeholder Engagement

Seeking advice from key stakeholders throughout the market access and reimbursement process can help identify potential barriers to a successful launch. Stakeholder engagement is particularly impactful when conducted early enough in the vaccine development program to allow the development and implementation of a robust evidence generation plan to overcome likely barriers.

Prepare: Key steps to prepare for market access include horizon scanning, early advice, strategic partnerships, and collaborations with key stakeholders to receive recommendations for inclusion in national immunization programs, NITAG/HTA review, and decision and procurement.

Innovate: There is a recognized need to improve market access processes for vaccines and pharmaceuticals. Innovative approaches that are being explored and/or implemented focus on promoting information sharing, resource sharing (e.g., via joint clinical assessment), overcoming funding and political barriers, and engaging with decision-making bodies to improve transparency (Case Study 4). The use of artificial intelligence (AI) is particularly topical in market access, and while its use in HTA and NITAG assessment remains limited, the technology is being increasingly exploited. AI has the potential to help accelerate vaccine market access and can be leveraged to conduct market research, optimize economic models, conduct systematic literature reviews, and develop submission documents. Nevertheless, the use of AI is associated with numerous challenges related to scientific rigor, reproducibility, and transparency, and its acceptability in HTA and NITAG assessment remains uncertain. Ongoing stakeholder engagement will be required to ensure that AI-driven evidence will be accepted by key decision-makers.[32]

Collaborate: Early engagement with key stakeholders is fundamental to creating a global market access strategy with key considerations and evidence generation planning to shape the environment. However, not all HTA bodies offer formal early advice, and of those that do, some will only provide advice for curative and not preventive vaccines. In such cases, informal advice may be sought by liaising with stakeholders through advisory boards. For best outcomes, it is critical to engage with experts who have extensive experience with HTA bodies and NITAGs.

Case Study 4: Stakeholder Engagement Led to a Reversal in a JCVI Statement Leading to the Adoption of a Vaccine in the UK

Background & Challenge

- A vaccine for group B meningococcal (MenB) was launched in the UK
- In July 2013, the JCVI released a statement advising against the introduction of routine immunization in infants and adolescents, claiming it was "highly unlikely" the routine immunization would be cost-effective (even at £0)
- The JCVI opened their conclusions to consultation

Approach

- Meningitis research foundation found that the cost-effectiveness analysis had underestimated burden of disease
- The manufacturer also raised concerns on one of the JCVI models, critiquing the lack of accuracy in capturing the true cost of surviving MenB and amputations
- The manufacturer further critiqued the lack of transparency on the rationale behind changes between earlier and later JCVI models and the lack of clarity on the factors considered by JCVI when assessing a vaccine (given they had not followed NICE methodology in certain aspects)
- The manufacturer also noted the potential negative consequences that the JCVI approach could have on future investments and on innovation in areas where the science is challenging and expensive and urged the government to align risks and rewards for the benefit of long-term public health

Impact

- The JCVI considered all the feedback and reviewed the modeling approach
- For the final recommendation, JCVI concluded that the vaccine could be cost-effective with a low vaccine price, leading to the introduction of the vaccine to the market

Abbreviations: JCVI = Joint Committee on Vaccination and Immunisation; NICE = National Institute for Health and Care Excellence

6. How will the EU's HTA Regulation Impact Vaccine Market Access Timelines?

In January 2022, the EU's Regulation[33] on HTA was adopted (hereafter referred to as "the Regulation"). The Regulation will become applicable in 2025 for oncology products and advanced therapy medicinal products and in 2030 for all new centrally approved medicinal products (including vaccines),[34] requiring them to undergo a joint clinical assessment (JCA) at the EU level. Joint scientific consultation for all products will commence in 2025.[34,35]

EU JCA reports are mandated to cover:

- The health problem and its current treatment
- A description of the health technology, along with its technical characteristics and relative clinical efficacy/effectiveness and safety[c]

EU JCA reports will not be mandated to include assessment of economic, social, ethical, and organizational factors, which will be considered at a national level. Decisions concerning national immunization programs, scheduling, price, and reimbursement will also remain at the national level and be based on local considerations.

This unified process of the Regulation could allow more consistent, transparent, and timely access to vaccines in the EU, and may help to overcome the substantial variation in methods and timelines that currently impede evaluation. In theory, the Regulation should speed up vaccine market access by removing the need for individual countries to perform a clinical assessment; however, it is unclear how timelines will be impacted. In addition, notable uncertainties remain regarding the JCA process. For example, although the specificities of vaccine HTA are acknowledged in Article 4 of the Regulation, no actions have yet been taken to implement these provisions. Uncertainties also remain regarding the impact of the Regulation on NITAG decision-making processes and timelines. Vaccine manufacturers should prepare for the effects of the EU's Regulation on NITAGs, for example, by seeking joint scientific consultation with the EU HTA body, which will become available in 2025.

Key Takeaways and Our Commitment

- Many factors contribute to delays in vaccine market access including, but not limited to, poorly transparent NITAG processes and requirements, time-consuming evidence generation requirements, and gaps and uncertainties in the evidence base.
- We have launched a "100 days to vaccine market access" initiative to help vaccine manufacturers submit a NITAG/HTA submission pack within 100 days of marketing authorization.
- Our recommendations focus on the implementation of a three-pillar "prepare, innovate, and collaborate" framework, which can be used to address HTA/NITAG submission requirements and overcome challenges throughout the vaccine lifecycle.
- We are committed to helping our partners to implement this framework, advocating for industry reform and seeking further opportunities to advance vaccine market access.

Limitations

This white paper focuses specifically on how vaccine manufacturers and their partners can accelerate vaccine market access by reducing the time between regulatory approval and the submission of a comprehensive NITAG/HTA evidence pack. This paper does not address other barriers to vaccine market access, such as affordability, supply and distribution challenges, vaccine hesitancy, infrastructure and healthcare system limitations, and global disparities. However, we acknowledge the critical importance of addressing these areas and recognize the need for reform to ensure equitable and widespread vaccine access.

c. While regulatory bodies focus on the clinical benefits of a health technology (notably safety and efficacy), the JCA, HTA, and NITAGs focus on the clinical, humanistic, and economic value relative to other licensed treatments. Consequently, JCA reports will include information on the burden of illness, current and proposed treatment pathway and relative efficacy, and effectiveness and safety data.

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