VACCINE INSIGHTS

VACCINE CLINICAL UPDATE

COMMENTARY

The new era of vaccines: scientific challenges and their regulatory needs

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The COVID-19 pandemic has confirmed that vaccines for infectious diseases have made the greatest contribution to global health of any intervention. On the other hand, it was not long ago that vaccines for cancer were just a dream for the future, whereas now they represent a viable option for active immunotherapy. Vaccines for the prevention of infectious diseases are referred to as traditional vaccines or prophylactic or preventive vaccines because they intend to directly prevent pathologies, whereas cancer vaccines are mainly therapeutic vaccines because they are used to treat cancer after it has already appeared. From the scientific point of view, both infectious and cancer vaccines aim to harness the immune system as part of the mechanism of action to achieve the therapeutic effect. Although for a long time the development of efficacious vaccines has relied on the better-known models of the immune response to infections, the recent breakthrough in cancer immunotherapy has disclosed the great advantage of sharing knowledge of host immunity to design novel vaccines. In addition, the recent remarkable technological advancements are now fostering a rapid evolution of the therapeutic potential of vaccinations. This new and vivid scientific landscape inevitably calls for a more suitable regulatory environment to promote the advancement in vaccines for infectious, degenerative and cancer diseases. Therefore, it has become urgent to clarify ambiguities in vaccinology, to absorb most meaningful scientific achievements in the processes for navigating the regulatory maze to bridge scientific challenges and regulatory needs.

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INTRODUCTION

The WHO defines vaccines as "biological preparations that improve immunity to a particular disease" underlying the fact that the immune system is the most important player determining the response to vaccines. Historically, the term vaccine has

been associated with infectious diseases, with prophylactic or preventive vaccines designed to prevent or reduce the severity of infection. These vaccines have been remarkably successful, saving millions of lives annually [1], and eradicating or drastically reducing diseases such as smallpox, polio, and measles. Although prophylactic vaccines are among the most effective tools for combatting infectious diseases, with efficacy rates exceeding 90% for illnesses like polio or measles, and over 75% for malaria and TB, efficacy among many old and emerging infectious diseases including Marburg virus disease, Lassa or Zika fever, continues to pose major global health challenges. In contrast to prophylactic vaccines, therapeutic vaccines are designed to treat established diseases, particularly cancer, by stimulating an immune response against malignant cells. Despite decades of research, the development of effective therapeutic cancer vaccines has proven exceptionally challenging. Early successes were largely limited to cancers associated with infectious agents: for example, the FDA-approved hepatitis B and HPV vaccines prevent liver and cervical cancers, respectively [2]. More recently, therapeutic cancer vaccines targeting non-viral cancers have been developed [3,4], including Sipuleucel-T (Provenge®) for metastatic prostate cancer and Talimogene laherparepvec (T-VEC®) for unresectable metastatic melanoma. These approaches illustrate the potential of immunotherapy but also highlight the complexity of translating preclinical success into clinically effective treatments.

A critical barrier to the development and adoption of cancer vaccines is regulatory complexity. Unlike traditional vaccines, therapeutic cancer vaccines face unclear regulatory definitions, extensive preclinical and clinical requirements, and stringent approval pathways that differ across regions. Regulatory challenges include establishing robust endpoints for efficacy, navigating combination therapy approvals, and demonstrating long-term safety in heterogeneous patient populations. These hurdles often delay clinical translation, increase costs, and limit patient access, even for vaccines with promising preclinical data.

The COVID-19 pandemic has revolutionized the vaccine field and demonstrated that accelerated regulatory pathways can dramatically shorten vaccine development timelines [5]. Applying these lessons to cancer vaccines requires aligning innovative therapeutic strategies with evolving regulatory frameworks to ensure safety, efficacy, and accessibility.

This review aims to clarify the key concepts in vaccinology needed to integrate emerging expertise from infectious diseases and cancer research with current regulatory processes. It highlights critical barriers in regulatory and clinical translation and discusses strategies to accelerate the development and advancement of these promising immunotherapies.

THE NEED TO CLARIFY REGULATORY AMBIGUITIES IN THE DEFINITION OF 'VACCINE'

The Oxford Dictionary reports that the noun vaccine originates from the late 18th century and derived from the Latin word 'vaccinus' , meaning 'of the cow' (vacca), referring to the early 'vaccine' use of dried cowpox virus lesions to protect against smallpox. In 1799, Edward Jenner used material from bovine scabs of ulcers caused by cowpox virus, also known as vaccinia virus, to inoculate children for the first time. However, the use of vaccinia scabs for immunization had been reported earlier by Lady Montague, wife of the English Ambassador to the Ottoman Empire [6], suggesting that the practice may have been imported from the Far East. Therefore, the first vaccines were based on inactivating the whole infective agent to reduce virulence, whereas modern vaccine

development often relies on recombinant viral material to obtain antigens capable of eliciting a targeted immune response. Nowadays, a vaccine is defined as a medicinal product whose mode of action consists of priming the adaptive immune system to recognize antigens expressed by a pathogen and protect the individual from the associated disease, consistent with definitions provided by EU [7] and FDA [8].

DIFFERENCE BETWEEN A 'CONVENTIONAL VACCINE' AND A 'CANCER VACCINE'

'Classical' prophylactic vaccines are usually intended to prevent the development of a disease in response to infection by priming the immune system to a rapid immune response. An important consideration (and frequent misconception, especially with SARS-CoV-2) is that vaccines do not always prevent infection but aim to control disease severity. Conventional vaccines are preventive, inducing adaptive immune response and long-term memory in healthy individuals to protect against future infections. Cancer vaccines, in contrast, are therapeutic, designed to stimulate the immune system against existing tumors, by targeting malignant cells. Searching for 'cancer vaccine' in PubMed from 2014 will retrieve more than 3,000 results. The term is catchy and clearly indicates the scope of these products, which leverage the individual's own immune system to fight cancer [9]. Tumors evade immune surveillance, requiring cancer vaccines to overcome mechanisms of immune suppression and escape [10]. These mechanistic differences between conventional and cancer vaccines shape their clinical development and regulatory pathways, with cancer vaccines specifically evaluated for inducing anti-tumor responses in patients, often alongside immune checkpoint inhibitors. Understanding these distinctions clarifies the unique positioning and challenges of cancer vaccines in immunotherapy.

For EU regulators, the term 'cancer vaccine' can be misleading because, by definition, vaccines are medicinal products intended to prevent infectious diseases, and cancer itself is not an infection. However, in some cases, cancer can result from previous or persistent infections—such as HPV, which may lead to cervical cancer. In these situations, medicinal products aimed at preventing cancer are classified as prophylactic vaccines, since their primary goal is to prevent the infectious agent rather than directly treat or target the cancer that may later develop. Conversely, the EU Regulation 1394/2007 clearly states that Advanced Therapy Medicinal Products (ATMPs) cannot be defined as vaccines if used for the treatment of non-infective diseases. The EMA defines immunotherapies as medicines that stimulate the immune system to kill the cancer cells [11]. Therefore, many innovative products such as tumor-specific T-lymphocytes, tumor-infiltrating lymphocytes, or CAR-T cells have been licensed as ATMPs rather than as vaccines [12]. Therefore, cancer vaccines are considered ATMPs and fall under the ATMP regulatory framework. In this review, the terms 'cancer vaccines' and 'ATMPs' are used interchangeably.

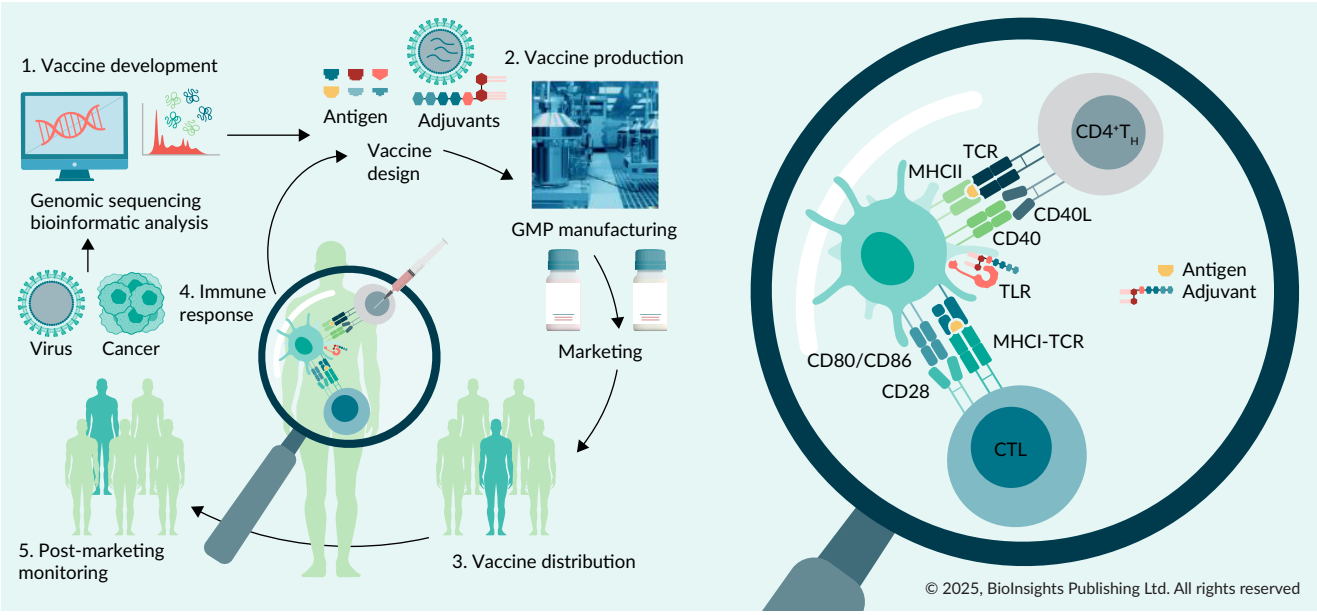
From a technological perspective, the advent of mRNA-based vaccines for active immunization against COVID-19 and their documented efficacy have generated considerable interest in mRNA-based therapeutics. Both Pfizer-BioNTech and Moderna leveraged previous experience developing mRNA cancer vaccines to accelerate the initial COVID-19 vaccine development. This has now come full circle, positioning mRNA technology as a key platform for producing vaccines against cancer [13]. mRNA technology allows for the rapid and precise design of vaccines by instructing cells to produce specific antigens that elicit targeted immune responses. In conventional vaccines, these pathogen-derived antigens are often well-characterized

and train the immune system to establish long-term protection against future infections. By contrast, cancer vaccines rely on tumor-specific antigens, frequently unique to an individual tumor, to activate immunity against existing cancers, highlighting their therapeutic rather than preventive role. Importantly, unlike conventional vaccines, cancer vaccines are often administered in combination with or as adjuncts to other therapies, such as immune checkpoint inhibitors (e.g., anti-PD-1 or anti-PD-L1). Current vaccine or ATMP regulations should be strengthened to address these considerations, supporting a regulatory framework tailored to the unique nature of cancer vaccines.

Both conventional vaccines and ATMPs require a clear description of identity and potency. Identity testing confirms that the correct active ingredient is present in the final product and refers to its composition, whereas potency is a measure of biological activity, informing the treatment dose and directly linking to therapeutic or prophylactic efficacy. For ATMPs such as vector–based vaccines, delineating identity and potency can be complex due to the highly composite molecular structure and antigenic properties of these biological products [14–16]. This complexity is further increased for cell-based ATMPs, such as dendritic cell (DC)–based vaccines, which exhibit high intrinsic variability due to factors such as lineage, differentiation stage, *in vitro* derivation, patient origin, and autologous or allogeneic status. Therefore, pre-defined variance in certain parameters

FIGURE 1

Schematic overview of the vaccine development process.



© 2025, BioInsights Publishing Ltd. All rights reserved. (1) Vaccine development: genomic sequencing and bioinformatic analyses identify antigens for infectious vaccines or tumor-specific neoantigens for cancer vaccines. Infectious vaccine antigens are typically derived from pathogens, whereas cancer vaccines target tumor-associated or patient-specific neoantigens. Adjuvants may be selected differently depending on whether the vaccine is prophylactic or therapeutic. (2) Vaccine production: identified antigens and adjuvants are formulated and manufactured under GMP conditions for both infectious (e.g., COVID-19) and cancer vaccines. (3) Vaccine distribution: vaccines are distributed to target populations, with infectious vaccines administered to healthy individuals and cancer vaccines to patients with established tumors. (4) Immune response: vaccines elicit antigen-specific immune responses; conventional vaccines stimulate long-term protective immunity, whereas cancer vaccines activate cytotoxic T lymphocytes to recognize and attack tumor cells. (5) Post-marketing monitoring: ongoing safety and efficacy monitoring occurs for both vaccine types. Differences in antigen selection, adjuvant use, and patient population reflect the distinct preventive versus therapeutic purposes of infectious and cancer vaccines.

should be accepted in the identity characterization of ATMPs. These factors should also be considered when defining potency, for which potency assays must be developed in accordance with product-specific EU regulatory guidance [17–20].

VACCINE INNOVATION BRIDGING SCIENTIFIC CHALLENGES

The novel immune concepts to bring into vaccine development

A fundamental grasp of certain pivotal mechanisms that drive the immune response is essential for expediting every stage of the vaccine development process, whether targeted at infectious agents or cancer (Figure 1).

The induction of specific adaptive immune response by vaccination is the key step for both eliciting long-lasting host resistance to infection or for eradicating cancer. The activation of both B and T cell arms of adaptive immunity is dependent on innate response. Over the past few years, the innate-adaptive immune paradigm has gained deeper knowledge, becoming a new source to improve vaccines. Successful vaccines activate innate immunity, and specifically DCs, which drive the generation of antigen-specific naive B and T cells, producing long-lived plasma cells, primary antibodies and memory B and T cells. This process, mostly achieved with the first vaccine immunization, generates resting trained innate cells, displaying memory-like features characterized by enhanced innate effector response upon restimulation able to strengthen the secondary effector and memory adaptive response, upon the vaccine boost dose [21]. Notably, both innate and adaptive immunity to vaccination are mediated by the activation of cellular signals governed by IFN type I (IFN-I) [22]. On the other hand, several intrinsic host factors, such as sex and age, may affect individual immune responses to vaccines.

In terms of sex differences, induction of toll-like receptor (TLR) and IFN-I pathways are greater in females than in males [23]. A positive regulatory feedback loop exists between 17β-estradiol-estrogen receptor-α (E2–ERα) and IFN-I signal in regulating the development and function of some DC populations. In particular, the activity of plasmacytoid DCs, which represent the central DC subset responsible for robust IFN-α production upon viral infection or vaccination, is under the control of TLR7, whose X chromosome-linked gene is regulated by E2–Erα [24]. Therefore, timing, and strong activation of innate immune response occurs more frequently in females, with the possibility to strengthen trained immunity to ensure a long-lasting state of activation of innate cells via epigenetic modifications and a prompter functional response upon reencountering antigen [21]. More vigorous adaptive immune responses are also observed in females than males. In addition, females usually develop higher antibody responses following vaccination against many viral infections such as influenza, HBV, yellow fever, smallpox, rabies, and HSV [25]. For T cell response, while males exhibit higher CD8+ and Treg cell counts associated with Th1 dominance, females have higher CD4+ T cell frequency combined with an increased CD4+/CD8+ T cell ratio, denoting Th2 prevalence. Therefore, females experience more robust T cell activation during infection and males may have weakened CD8+ T cell function in an androgen receptor androgen receptor-dependent manner [26]. In the light of all this, it is worth emphasizing that several genes directly and indirectly regulating B and T cell function are located on the X chromosome and may escape the dosage-compensation inactivation mechanism [27]. Importantly, these mechanistic and immunological differences are supported by clinical and epidemiological evidence showing sex-specific variations in vaccine efficacy, immune

response magnitude, and immune-related adverse events (irAEs). For instance, females often develop higher antibody titers and more robust cellular responses to vaccines and immunotherapies, whereas they may also experience irAEs at higher rates than males. These observations highlight the need to consider sex as a critical factor in vaccine design, immunotherapy trials, and risk assessment for adverse events [28,29].

The variability in immune responses is also shaped by age, as both development and aging influence immune function. Early infants develop very short-lived immune responses to vaccines, likely due to the interference of maternal antibodies and the immaturity of their immune systems. In contrast, older children mount stronger and more durable immune responses as their lymphoid tissues and immune cell populations mature, allowing for more effective T and B-cell activation and memory formation [25]. For instance, BCG vaccination elicits stronger protection in children than in adults, which has been attributed to the early establishment of trained immunity and the greater plasticity of the developing immune system [30]. Epidemiological studies further support these age-dependent differences, showing higher vaccine efficacy and lower incidence of infectious diseases in older children compared to infants [31].

With aging, immune function gradually declines, a process known as immunosenescence, while chronic low-grade inflammation, or inflammaging, increases. Immune changes in older adults are highly heterogenous due to lifelong exposure to pathogens, environmental stressors, and other harmful stimuli, yet some traits consistently differ between sexes. These age-related alterations reduce vaccine responsiveness, resulting in weaker antibody production, impaired T cell function, and diminished long-term protection [32]. Elderly females typically experience a slower decline in T and B-cell functions with higher IL-10 production, which helps limit inflammaging, whereas older males show greater chronic inflammation due to persistence of high monocyte activity and inflammation [33]. Consequently, most vaccines provide limited protection in the elderly, despite general immune response in females. Therefore, incorporating the full spectrum of sex- and age-dependent immune factors is crucial for developing vaccines that provide robust and long-lasting immunity.

These concepts emphasize the need to adopt different strategies for obtaining a successful vaccination, defined as an efficacious and balanced immune response in the specific target population. For example, rethinking the best doses as well as the immunization schedules of vaccines across the course of life could maximize the protective effects while limiting adverse events. For example, since adult females typically have stronger immune responses, they could potentially benefit from lower doses of vaccines. Likewise, designing a next generation of vaccines adjuvanted with substances able to target additional signals of the immune system could overcome the unresponsiveness of elderly people. Therefore, fostering better knowledge of individual mechanisms paves the way for safer and more efficacious vaccines in the future.

Exploitation of vaccine-induced immunity by adjuvants

Adjuvants are one of the most crucial components of vaccine formulations, strengthening the immune response to vaccination in terms of magnitude and durability. Despite the intense effort of the research community, to date only six different adjuvants have been licensed by the regulatory authorities to be incorporated into authorized vaccines in many parts of the world. The revolution in the field has come from the recent deeper understanding of the fine mechanisms regulating

the immune response, and in particular innate immunity, providing new avenues for developing novel adjuvants with the potential to generate superior immunity ensuring safety while limiting toxicity.

Adjuvants can be classified as immunostimulants and delivery systems [34]. Immunostimulants function as agonists of TLRs, cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING), c-type lectin receptors (CLRs) and other pattern recognition receptors (PRRs), and include agents such as cytokine, monophosphoryl lipid A (MPL) and CpG. By triggering these signals, adjuvants target innate immune cells promoting the activation of antigen presenting cells (APCs), such as DCs, via stimulation of intracellular pathways that reinforce MHC-dependent antigen presentation and cytokine production. Thus, these signals operate synergically to both induce antigen-specific T cell activation and support antibody class switching in B-cells amplifying the antibody response [35]. Ideally, a vaccine formulation which contains the appropriate antigen, per se poorly immunogenic, and a suitable immunostimulant has the potential to properly stimulate a specific and efficacious immune response. One example of an authorized product with this kind of adjuvant is Heplisav B which consists of hepatitis B surface antigen (HBsAg) adjuvanted with CpG 1018. An important consideration for the historical development of hepatitis B vaccines was also the recognition that, in addition to adjuvants, the self-assembly of HBsAg into larger particles was important for potency [36].

Delivery systems include polymer-based systems, such as aluminum salts and poly(-lactide-co-glycolide) (PLGA), as well as lipid-based systems, such as lipid nanoparticles. Antigens absorbed onto aluminum salts are the most commonly used delivery systems for commercially approved vaccines including Engerix B (purified recombinant hepatitis B surface antigen that contains aluminum oxide) and HBVaxPro (HBsAg adsorbed on amorphous aluminum hydroxyphosphate sulphate), amongst others. Delivery systems are designed to increase antigen uptake and presentation by DCs in order to promote stronger antigen-specific adaptive immunity. Specifically, delivery systems modulate the release of antigens by several processes including the extension of their bioavailability via cargo protection, the targeting of APC-specific receptors, the enhancement of cargo trafficking to lymph nodes, and the increase of antigen cross-presentation. Therefore, delivery systems enhance vaccine targeting of innate immune cells, reinforcing their capability to promote robust cellular and humoral responses [37]. In addition, there are the so-called 'adjuvant systems' that consist of the combination of immunostimulants and delivery systems. One example is AS04, which is composed of MPL absorbed onto aluminum hydroxide and is a component of the approved vaccine Cervarix (HPV type 16 and type 18 L1 proteins).

In this complex landscape, given that the main goal of any adjuvant is to enhance the innate immune functions in order to stimulate efficacious and long-lasting antigen-specific adaptive immune responses, it is crucial to advance vaccine formulations, selecting suitable adjuvant to be combined with specific antigens. Therefore, to maximize vaccine design, key issues relating to the features of the vaccine-induced immunity need to be considered. For example, the time-dependent difference of action between antigens and adjuvant at the site of immune reaction may raise the constraint on the specific vaccine formulation for modulating antigen release, or the immunogenic potency of a particular antigen may require the use of a specific adjuvant. Overall, the number of approved adjuvants is still limited, although some experimental adjuvants are still being tested in trials. Since adjuvants are intimately linked to

vaccine manufacturing and quality, there is often limited data comparing similar vaccines adjuvanted differently such that comparative mechanism, safety, and efficacy are often lacking [38].

From the regulatory point of view, the exploitation of these research topics is extremely challenging since adjuvants are not licensed on their own but as a component of a specific vaccine. Consequently, preclinical testing for evaluating the safety and potency profile of adjuvants needs to be tailored to the specific product on a case-by-case basis. Particularly important are toxicology studies aimed at confirming that adjuvants do not adversely alter the safety or potency of the vaccine by inducing unwanted events such as hyper-inflammation and excessive cytokine production causing reactogenicity with break of immune self-tolerance [39]. Nowadays, the gained technological and scientific knowledge in the field of vaccines has broken new ground for using novel adjuvants rather than classical adjuvants to develop more potent vaccine formulations for infectious and cancer diseases. However, expediting the development of new adjuvants from the initial hypothesis to the regulatory process for clinical use demands robust mechanistic insights into the targeted immune response.

HOW TO NAVIGATE THE REGULATORY MAZE IN VACCINE DEVELOPMENT

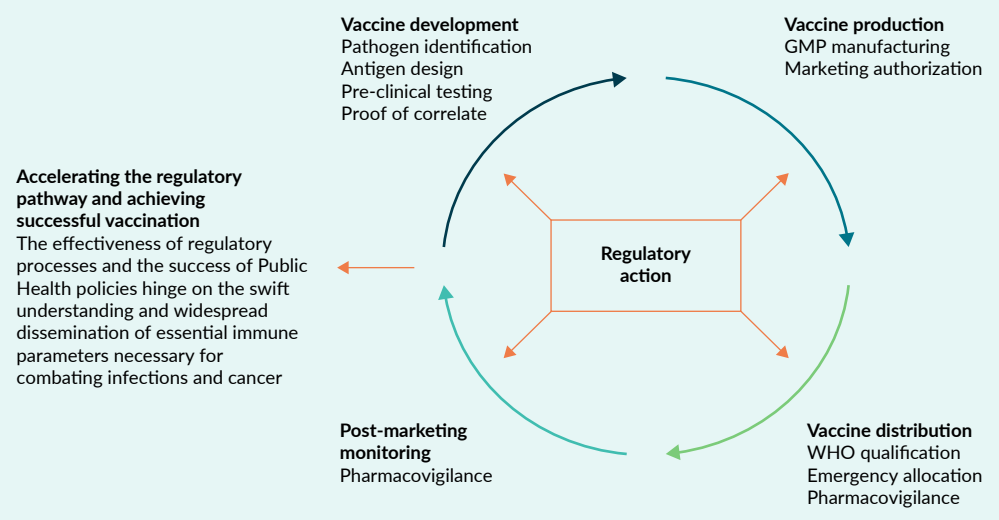
Ensuring a timely alignment between the regulatory process and each phase of vaccine development is critical for generating an effective product. This ensures a balance between scientific effort and economic commitment, facilitating an effective vaccine for administration to diverse groups of individuals, both in routine circumstances and during pandemics (Figure 2).

The regulatory pathway to develop a novel vaccine was well described and historically well-trodden until a new generation of vaccines based on the use of RNA to encode the desired antigens directly within the recipient cells won the race for the prophylaxis of COVID-19. A new set of guidelines will now be critical to deal with the technical specifications of this new class of products [40]. However, the development path remains unchanged, as a vaccine is considered a medicinal product and as such is covered by the relevant legislations and guidelines specifically designed for the development of medicinal products. In particular, it requires a marketing authorization to be commercialized. The European marketing authorization is released by the European Commission on recommendations from the EMA while in USA it is covered by the FDA. In both cases, the process leading to the marketing authorization of vaccines for infectious diseases is focused on establishing a positive risk/benefit ratio and demonstrating non-inferiority compared to existing treatments. The efficacy of a vaccine is clinically tested by treating a healthy population that could be exposed to the infective pathogen and then comparing the rate and severity of disease between treated and untreated subjects.

In fact, prophylactic vaccines do not prevent infection itself but rather the pathology resulting from the infection. To design the most effective development plan for a new vaccine, various information is required, as set out in the guidelines provided by EMA [41]. Several crucial factors to be considered include the nature of the infective agent, its epidemiology, potential carriers, and the mode of transmission. Similarly, critical parameters like the frequency and intensity of epidemics, pinpointing the target population for vaccination, understanding their environment, and planning the logistics for distribution and administration, play a significant role in shaping of the development approach. In addition, economic issues as well as cost and reimbursement

FIGURE 2

Summary of the regulatory process in vaccine development.



The figure illustrates regulatory actions across key stages, from early research through clinical development to marketing authorization, showing how scientific and economic considerations are coordinated. It covers both infectious disease vaccines, typically administered to healthy populations for prophylaxis, and therapeutic cancer vaccines, which are given to patients with established disease. Notably, differences in trial design, efficacy evaluation, and risk/benefit assessment between these two vaccine types exist, emphasizing the need for tailored regulatory strategies for cancer vaccines.

policies are factors to be considered before initiating vaccine development.

When translating these principles to cancer vaccines, several fundamental differences arise. Unlike prophylactic vaccines, therapeutic cancer vaccines are administered to patients with established disease, meaning the clinical objectives focus on disease regression, control, or improved survival rather than prevention. Consequently, efficacy evaluation, risk/benefit assessment, and trial design are substantially more complex. Patient heterogeneity, tumor microenvironment, prior therapies, and disease stage can all affect outcomes and must be carefully considered in regulatory submissions. These challenges highlight the need for tailored guidelines for therapeutic cancer vaccines that differ from those used for infectious disease vaccines, including the design of adaptive clinical trials, incorporation of surrogate endpoints, and integration of biomarker-based patient selection.

As of January 2025, the new EU Health Technology Assessment Regulation (HTAR) 2021/2282 became applicable to marketing authorization applications for new cancer medicines or ATMPs. The new HTAR rules will also be extended to orphan medicines in January 2028. This has immediate implications for cancer vaccines, as early-stage clinical development for such products, even for experimental therapies, should now also consider developing data to support future HTA interactions. Tailored regulatory strategies that address the unique challenges of therapeutic cancer vaccines are increasingly necessary to ensure both timely approval and alignment with health technology assessments.

Development of prophylactic vaccines

The developmental pipeline of a prophylactic vaccine, particularly for emerging infectious diseases, is inherently complex,

starting with the identification of the pathogen. From identifying a new disease to collecting biological samples and isolating the agent, a chain of events needs to take place. First, transporting samples to specialized laboratories is possible but requires that the collection process supports the preservation of the integrity of the infectious agent, implying recognition of the uniqueness of the condition. Subsequently, the identification of new pathogens must be exceptionally precise, resulting in distinct outcomes. In this context, the introduction of cheap DNA/RNA sequencing technologies can facilitate rapid identification, though they are currently accessible primarily in advanced economies. Once the genome of the agent is identified, *in silico* technologies can be applied to identify structural components of the antigen, pinpoint potential targets for inhibition, and assist in design of the vaccine. This method is considerably faster than the traditional approach, which requires cultivating the infective agent in a suitable host, either *in vitro* or *in vivo*, followed by purification and characterization. A requirement for this fast approach is to have predictive assays in place that can effectively reflect major vaccine efficacy (correlate of protection) and indicate potential safety issues (e.g., excessive inflammation) or immune evasion effects. This usually requires a solid understanding of the pathogen, the disease, and its immune evasion strategies. Once the vaccine is formulated with the addition of an adjuvant and excipients, where applicable, considerations regarding the target, logistic constrains, and economic factors will guide the definition of the desired final characteristic of the product. Therefore, a suitable manufacturing process can be planned and executed, and the initial batch can undergo *in vitro* testing for purity and suitability. Depending on the characteristics of the disease, an appropriate *in vivo* animal model is selected, and a proof of principle for efficacy is obtained.

In the clinical development of vaccines for infectious diseases, obtaining authorization to conduct clinical trials with a large number of healthy volunteers is crucial, and requires providing preclinical data that assess the safety of the product and a proof of principle, demonstrating its ability to elicit an immune response and offer protection in an adequate animal model. The authorization to treat healthy individuals with a new vaccine is released by the national competent authorities based on the evaluation of the risk/benefit ratio. The quality and safety data are also required to assess a new vaccine and to define the initial dosage for the first in human clinical trial. Nevertheless, for non-endemic pathogens, such clinical trials need an epidemic scenario, as observed for example in SARS coronavirus in 2003, H1N1 in 2009, MERS in 2015, and notably the global health emergency of SARS-CoV-2 in 2019. In each of these instances, central to the required clinical data are i) the backward pathway for establishing quality and safety requirements and ii) the identification of an appropriate correlate of protection.

Development of therapeutic vaccines for cancer

The mode of action of a therapeutic vaccine is still based on the immune recognition of a target based on anomalous antigen expression, including tumor-associated antigens and tumor-specific antigens. Cancer cells evade immune clearing through multiple mechanisms, such as downregulation of MHC molecules, expression of immune checkpoint inhibitors (e.g., PD-L1), and recruitment of immunosuppressive cells, which collectively dampen anti-tumor immunity. To overcome these barriers, cancer vaccines may employ autologous cells, engineered components, or synthetic constructs designed to enhance immune activation. AI tools are increasingly being used to design synthetic immunogens or

receptors and to predict immune responses, potentially streamlining vaccine development and informing alternative nonclinical models [42]. However, the validation of AI-driven designs and their regulatory acceptance remain areas of active investigation. Despite these innovations, therapeutic cancer vaccines must comply with established medicinal product regulations. At the time of marketing authorization, they require clear definitions of identity (precise characterization of the active components), potency (ability to elicit the intended immune response), and mode of action (mechanistic basis for the therapeutic effect), ensuring safety, reproducibility, and efficacy in patients. The identity of cell-based medicinal products is addressed in the EMA Guideline On Human Cell-Based Medicinal Products [43]. Due to the complexity of cell populations, it is defined through a combination of biomarkers, biological functions, capacities, and the specific manufacturing process. Potency is often challenging to assess *in vitro* and may require validated surrogate biomarkers for timely assessment. A common approach in cancer immunotherapy is to use autologous cells equipped with a recombinant antigen receptor to directly eliminate target cancer cells, such as in CAR-T therapies. These genetically modified autologous cells are considered gene therapies and must follow the Guideline On Quality, Non-Clinical And Clinical Aspects Of Medicinal Products Containing Genetically Modified Cells [44] where applicable.

Preclinical and clinical study requirements are further detailed in the Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials [45]. Unlike prophylactic vaccines, clinical development for therapeutic cancer vaccines involves patients rather than healthy volunteers, with the primary endpoints focusing on survival or complete remission and often requiring prolonged follow-up to confirm durable responses and non-recurrence.

Importantly, therapeutic cancer vaccines require special consideration during marketing development due to their unique characteristics. They are typically patient-specific, administered in hospital settings, and demand stringent storage and logistic conditions because of their short shelf-life and sensitivity to environmental factors. Their cost per unit is substantially higher than conventional vaccine and they are associated with an increased risk of complication for patients. Additional challenges in cancer vaccine design involve the need to overcome immune tolerance while minimizing the risk of autoimmunity. As scientific knowledge advances, greater personalization of vaccine design may become possible, targeting novel antigens and potentially pushing the limits of predicted immunogenicity and mechanism of action. Potential risks, such as autoimmunity or other irAEs, should be carefully evaluated based on experience from related products, highlighting the importance of collaboration to advance the field and ensure patient safety.

CONCLUSION

The COVID-19 pandemic has shown that vaccine development can be significantly accelerated when regulatory processes are streamlined and coordinated with scientific innovation. A central lesson is the importance of understanding the immune mechanisms underlying vaccine responses, particularly in specific target populations, to guide the design of next-generation vaccines. This requires precise definitions of vaccines, the knowledge of their mode of action, and the rational use of advanced adjuvants to optimize immune responses. Despite these advances, substantial uncertainties remain, including the challenges of navigating complex regulatory frameworks

and addressing emerging societal factors such as vaccine hesitancy, global migration, and the impacts of climate change. To overcome these challenges, early and continuous dialogue among all stakeholders, including regulators, developers, manufacturers, and policymakers, is essential. Structured collaboration and effective communication platforms can bridge scientific, regulatory, and societal considerations, ensuring that vaccines are developed efficiently, safely, and equitably. In summary, the actionable takeaway is that future vaccine development must integrate scientific innovation, regulatory preparedness, and societal awareness into a coordinated framework. This approach will enable rapid, safe, and effective responses to both emerging infectious diseases and the growing field of therapeutic vaccines, ensuring public health needs are met proactively and efficiently.

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AUTHORSHIP & CONFLICT OF INTEREST

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