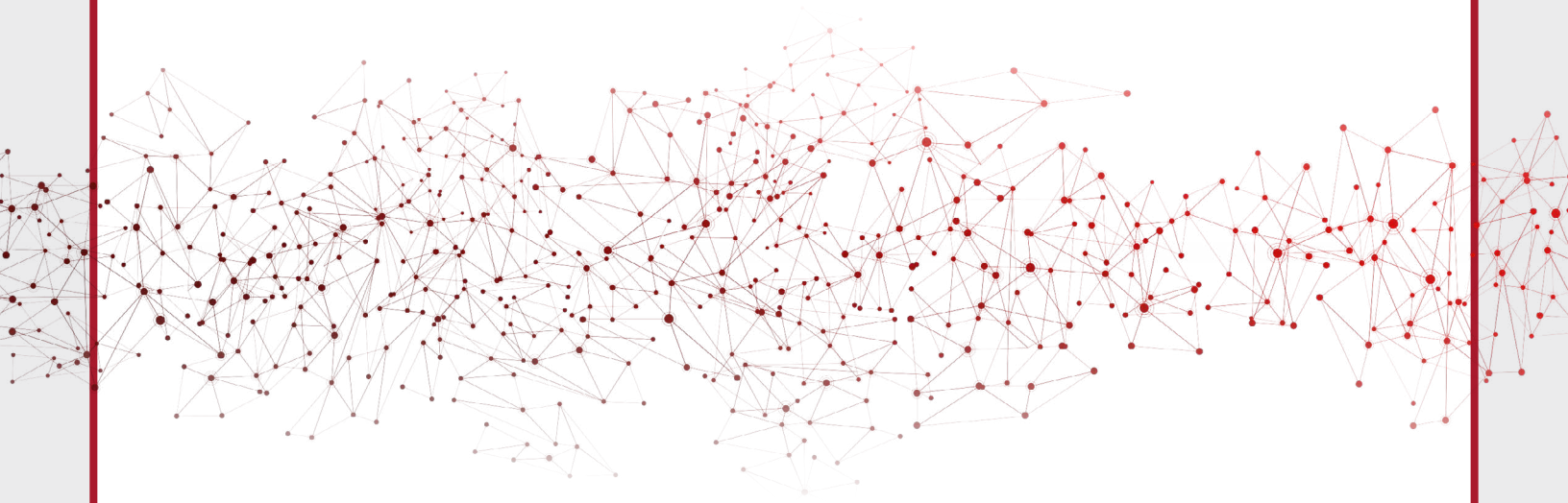
TECH FACTSHEETS FOR POLICYMAKERS

FALL 2020 SERIES

Vaccine Platforms



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The Technology Factsheet Series was designed to provide a brief overview of each technology and related policy considerations. These papers are not meant to be exhaustive.

Technology and Public Purpose Project

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Executive Summary

A **vaccine platform** is a "plug -and-play" physical framework that can be used when developing vaccines for emerging infectious diseases, such as COVID-19. Vaccine platforms use a base carrier or "vehicle," such as a nucleic acid, viral vector, or liposome, which can be used interchangeably for various diseases. Once designed and licensed for one vaccine, the development of future vaccines using the same platform would simply require substituting the desired antigenic component, or a genetic compound that normally triggers an immune response. This would enable faster and cheaper development, regulatory approval and mass production.[1][2] Terms such as *plug-and-play* and *cartridges* are often used to describe the functionality of vaccine platform technology.[3]

The development of vaccine platform technologies presents both risks and opportunities. These technologies have the potential to aid in developing vaccines for a variety of existing and emerging diseases. In addition, traditional vaccine development often takes years or even decades, but the versatility and sustainability of platform technologies may allow this process to be substantially streamlined. If successful, this could facilitate pandemic responses and help to mitigate widespread losses like those seen in the recent COVID-19 pandemic. However, there are concerns about the potential for unknown and dangerous side effects associated with platform technologies. In addition, the funneling of resources and funding into novel vaccine platforms could compete with and decrease access to traditional vaccines that remain vital for the prevention and treatment of disease.[4]

In the United States, there is no legislation specific to vaccine platforms, but a variety of federal laws relating broadly to vaccines and other biological products are applicable. In addition, the Food and Drug Administration (FDA), and the United States Department of Agriculture (USDA), which are responsible for vaccine market approval for humans and animals, respectively, have various guidelines that refer, at least in part, to platform technologies. The World Health Organization (WHO) also has various guidelines for all of its member countries that deal with the research, manufacturing, and regulation of vaccines, including some that are specific to products using platform technologies.

Given the rapidly evolving innovation associated with vaccine development, particularly in response to pandemic situations like COVID-19, there is a need for policymakers to understand the potential risks and benefits of platform technologies.

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1 Shere, Jack, A. "Veterinary Services Memorandum 800.213." United States Department of Agriculture, 2015. Available Online. https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_213.pdf

2 World health Organization Expert Committee on Biological Standardization. "Guidelines on the quality, safety, and efficacy of respiratory syncytial virus vaccines." November, 2019. Available online. https://www.who.int/biologicals/expert_committee/RSV_Guidelines_POST_ECBS.PDF?ua=1

3 https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf

4 Ibid.

What are Vaccine Platforms?

Vaccines provide protection against disease by stimulating immune responses to foreign material in the body, such as a virus. In response to the presence of foreign proteins called antigens, B cells produce antibodies that are capable of recognizing, binding, and marking antigens on attacking or infected cells for destruction by T-cells. After exposure to antigens, some T cells are also capable of recognizing and attacking the antigens on infected cells upon subsequent exposure. Thus, vaccines are intended to produce a period of extended immunity.

According to the WHO and FDA, **vaccine platforms** allow different antigens to be inserted into a common vector or expression system backbone (the "platform") in order to make various recombinant vaccine products.[5][6] The term 'vaccine platform' is used quite ambiguously and can be applied to a spectrum of technologies for producing and delivering vaccines, each with its own advantages and disadvantages.[7] Despite being so different, all vaccine platforms share the characteristic of being *pluripotent*, or broadly applicable to various diseases. This is in contrast to traditional mechanisms of vaccine production, which are only suitable for a single disease application, such as the annual flu strain.

Vaccine platforms also present an alternative to traditional whole-pathogen vaccines because they only use pieces of a germ – like its protein, sugar, or capsid (casing around the germ). There are two main types of whole-pathogen vaccines: inactivated whole-pathogen vaccines contain pathogens that have been killed with heat, radiation or chemicals, while live-attenuated whole-pathogen vaccines contain a version of the pathogen that has been weakened. In both cases, the pathogen is sufficiently altered so that it cannot cause infection. Although there are many successful whole-pathogen vaccines on the market, platform technologies provide a potential alternative for the prevention and treatment of novel diseases or for full pathogens that are too risky to use in vaccines, even in an attenuated form, such as HIV.

Vaccine development often takes years, but the versatility and sustainability of platform technologies may allow this process to be substantially streamlined. If successful, this could facilitate pandemic responses and help to mitigate widespread losses like those seen in the COVID-19 pandemic.

5 Shere, Jack, A. "Veterinary Services Memorandum 800.213." United States Department of Agriculture, 2015. Available Online. https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_213.pdf

6 World health Organization Expert Committee on Biological Standardization. "Guidelines on the quality, safety, and efficacy of respiratory syncytial virus vaccines." November, 2019. Available online.

7 Adalja, Amesh, A., et al. "Vaccine Platforms: State of the Field and Looming Challenges." Johns Hopkins Bloomberg School of Public Health: Center for Health Security, 2010. Available Online. https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf

Types of Platforms

- **Viral Vector.** Viral vector vaccine platforms utilize viruses in which viral genes have been replaced with a gene of interest that encodes a particular antigen. The two main types of viral vector vaccines are replication-competent and replication-incompetent. The immune response of replication-competent viral vectors depends on its ability to fully replicate in order to express the gene for the antigen. In contrast, replication-incompetent viral vectors can produce an immune response without replication and therefore do not cause an active infection.[8] The most common viral vectors are vaccinia and adenovirus, but a variety of other viruses are also used.[9] Viral vector vaccines generally have a higher immunogenicity than traditional vaccines, but they also carry potential risks of recombination, reversion to a virulent form, and viral evolution that results in elimination of the transgene of interest.[10] [11]

- **Expression System.** Expression systems are genetic constructs that are engineered to produce an antigen. Generally, a recombinant viral vector is created with an 'expression cassette' that codes for the antigen of interest. This virus is used to infect cells and the cell line is used to produce the antigen which can then be purified and used in a vaccine.[12] Insect, mammalian, plant, bacterial, and yeast cells can all be used in an expression system. One particularly common expression system is the baculovirus expression system in which baculovirus is used to produce antigens in insect cells. Each type of cell line has its own strengths and weaknesses, but one common problem is that immunogenicity of the vaccine may be decreased if the structure of the antigens that are produced by the expression system is not the same as it would be in human cells.[13]

- **Nucleic Acid.** Nucleic acid vaccine platforms use DNA or RNA that codes for a particular antigen.[14] Although DNA is more stable, RNA platforms may be preferred to DNA platforms because DNA must cross both the cellular and nuclear membranes, while RNA can remain in the cytoplasm and only needs to cross the cellular membrane.[15] RNA vaccines can be further subdivided into synthetic

8 Adalja, Amesh, A., et al. "Vaccine Platforms: State of the Field and Looming Challenges." Johns Hopkins Bloomberg School of Public Health: Center for Health Security, 2010. https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf

9 Takehero, Ura, et al. "Developments in Viral Vector-Based Vaccines." Vaccines, 2014. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494222/

10 Choi, Youngjoo and Chang, Jun. "Viral vectors for vaccine applications." Clinical and Experimental Vaccine Research, 2013. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3710930/

11 Bull, James, B., et al. "recombinant vector vaccine evolution." PLoS Computational Biology, 2019. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6668849/#:~:text=Author%20summary,we%20want%20to%20generate%20immunity.

12 Fisher, DI., et al. "Expression Systems." Encyclopedia of Cell Biology: Volume I, 2016. Available Online. https://www.sciencedirect.com/science/article/pii/B9780123944474100094

13 Van Oers, Monique, M. "Vaccines for Viral and Parasitic Diseases Produced with Baculovirus." Advances in Virus Research, 2006. Available Online. https://www.sciencedirect.com/science/article/pii/S0065352706680068?via%3Dihub

14 Restifo, NP., et al. "The promise of nucleic acid vaccines." Gene Tehrapy, 2008. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241736/

15 Adalja, Amesh, A., et al. "Vaccine Platforms: State of the Field and Looming Challenges." Johns Hopkins Bloomberg School of Public Health: Center for Health Security, 2010. Available Online. https://www.centerforhealthsecurity.org/our-work/pubs_archive/

mRNA vaccines and self-amplifying RNA vaccines. Synthetic mRNA results in immediate translation of the antigen, while self-amplifying RNA amplifies itself prior to translation. While both achieve similar levels of immunogenicity, self-amplifying mRNA requires a lower dosage.[1617]

- Nucleic acid platforms have many advantages, including greater control over the presentation of the antigen to the immune system, and the ability to manufacture the vaccine without any viral products that might be hazardous or compete with the antigen for immunodominance. However, the technology is still in the fairly early stages, and more research needs to be done to confirm the safety and efficacy of nucleic acid platforms. For example, although they are generally considered very safe, DNA vaccines have the underlying risk of anti-DNA autoimmune responses or integration of viral DNA into the host's chromosomes.[18] [19]

- **Emerging Platforms.** The above three categories constitute the main types of vaccine platform technology. However, researchers are also developing novel platforms for future use. For example, a research team at the Wyss Institute at Harvard University is working on a "first-in-class immuno-material-based" vaccine platform called OMNIVAX. Upon injection, the vaccine forms a scaffold that attracts dendritic immune cells and programs them to respond to a specific antigen. The cells are then released, and they migrate to nearby lymph nodes where they facilitate a systemic and prolonged immune response. Using modular technology, multiple antigens can be incorporated into a single OMNIVAX vaccine.[20] Other organizations are also developing their own novel platforms, but they all share the basic goal of developing a method of creating versatile "plug-and-play" vaccines.

pubs-pdfs/2019/190423-OPP-platform-report.pdf

16 Pardi, Norbert, et al. "mRNA vaccines- a new era in vaccinology." Nature Reviews Drug Discovery, 2018. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5906799/#R52

17 Vogel, Annette, B., et al. "Self-Amplifying RNA Vaccines Give Equivalent Protection Against Influenza to mRNA Vaccines but at Much Lower Doses." Molecular Therapy, 2018. Available Online. https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(17)30594-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1525001617305944%3Fshowall%3Dtrue

18 Restifo, NP., et al. "The promise of nucleic acid vaccines." Gene Tehrapy, 2008. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241736/

19 Vogel, Frederick, R. and Sarver, Nava. "Nucleic Acid Vaccines." Clinical Microbiology Reviews, 1995. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC174632/pdf/080406.pdf

20 Wyss Institute. "OMNiVAX: Broadly Deployable Infection Vaccine Platform." https://wyss.harvard.edu/technology/omnivax-broadly-deployable-infection-vaccine-platform/

Related Technology

Vaccine Platform technologies often utilize genetic engineering, which is defined as the "process of using recombinant DNA technology to alter the genetic makeup of an organism."[21] This is distinct from artificial selection in which organisms are selectively bred to perpetuate certain traits. Genetic engineering involves deliberate manipulation of an organism's genetic sequence.[22] Vaccines created using platform technology may be recombinant DNA or RNA products, which also makes them Genetically Modified Organisms (GMOs).

Like vaccine platform technology, gene therapy also utilizes genetic engineering. While not currently used in use, gene therapy is a field of emerging medical technology that involves using genes to prevent or treat disease. This could occur by replacing a mutated gene with a healthy copy, creating a gene "knockout" by inactivating an unhealthy gene, or by introducing a novel gene.[23]

Limitations

Vaccine platforms offer a promising alternative to traditional vaccine technologies. However, much of the technology is still new and very few vaccines using platform technology are available on the market. More pre-clinical and clinical research is needed to determine the safety and efficacy of various platforms and the situations in which each should be used.

In addition, although it could be beneficial for platform technologies to facilitate the vaccine approval process, particularly in epidemic or pandemic situations, current regulations surrounding vaccine development do not allow this. In the interest of ensuring safety and efficacy, regulatory bodies evaluate a specific vaccine product and not the development process, so the successful use of a vaccine platform in one instance would not allow new vaccines using the same platform to get any sort of pre-approval.[24] There is also no guarantee that a platform will work for a specific vaccine, even if it has been successfully used in the production of other vaccines. Platform technologies may still speed up preclinical development and manufacturing processes, but they will not necessarily speed up clinical trials or FDA approvals.

21 National Human Genome Research Institute. "Genetic Engineering." https://www.genome.gov/genetics-glossary/Genetic-Engineering

22 Ibid.

23 Genetics Home Reference. "What is gene therapy?" July 7, 2020. https://ghr.nlm.nih.gov/primer/therapy/genetherapy

24 Adalja, Amesh, A., et al. "Vaccine Platforms: State of the Field and Looming Challenges." Johns Hopkins Bloomberg School of Public Health: Center for Health Security, 2010. Available Online. https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf

Current Applications and Market Development

Although vaccine platform technologies are diverse, they constitute somewhat of a niche market because they are solely used for the production of vaccines. Vaccine platform technologies are used to treat and prevent various diseases in both humans and animals.

Healthcare

The main market for vaccine platforms is human healthcare. They can be applied to the treatment and prevention of a wide range of health concerns, including:

- Infectious diseases: COVID-19, SARS, MERS, TB, Influenza, HIV, Ebola, Zika etc.
- Parasitic diseases: Malaria, Leishmaniasis, Chagas, etc.
- Cancer: melanoma, colectorel cancer, prostate cancer, etc.
- Autoimmune diseases: type I diabetes, rheumatoid arthritis, celiac disease, etc.
- Allergies: birch, Japanese cherry blossom, cat dander, dust-mite, etc.

The application of vaccine platform technology is especially promising for public health responses to novel diseases that have epidemic or pandemic potential such as Ebola, Zika, or COVID-19. Due to the potential for platform technologies to speed up the development process of vaccines, they have the potential to facilitate the response to an emerging disease. Typically, the process for developing a viral vaccine using the traditional live-attenuated or killed pathogen is a 15 to 20 year timeframe from the discovery of the virus to the availability of the vaccine on the market.[25] With this timeline, by the time the vaccine is finally available, the outbreak may have already resulted in significant rates of infection, loss of human life, negative economic implications, etc. Using DNA vaccines, the National Institute of Allergy and Infectious Disease (NIAID) Vaccine Research Center reduced the time from identification of the target viral sequence to initiation of phase 1 clinical trials from 20 months to just over 3 months, which would make a significant difference in a pandemic.[26]

25 Graham, Barney, S., et al. "Novel Vaccine Technologies: Essential Components of and Adequate Response to Emerging Viral Diseases." JAMA Network, 2018. Available Online. https://jamanetwork.com/journals/jama/fullarticle/2676502

26 Ibid.

Food and Agriculture

Aside from their potential use in veterinary medicine, vaccine platforms may also be used to combat diseases that are common in animals used as livestock. For example, Type A Influenza can decimate swine and poultry populations. The development of an Influenza vaccine using platform technology would help to avoid the massive losses that occur as a result of disease outbreaks. [27]

Market Landscape

Products using vaccine platform technologies are produced primarily by pharmaceutical and biotechnology companies. Some of the most prominent private-sector manufacturers of these products include GlaxoSmithKline, Merck and Co, Sanofi, Pfizer, Novavax, Emergent BioSolutions, CSL Limited, Inovio Pharmaceuticals, Bavarian Nordic, and Mitsubishi Tanabe.[28]

Universities and hospitals may also engage in vaccine research and development, but they typically rely on outside manufacturers for production. For example, to combat both the University of Queensland and Oxford University developed high-profile COVID-19 vaccine candidates. However, they plan to rely on CSL and AstraZeneca, respectively, to manufacture their vaccines.[2930]

There are also smaller biotechnology startups that develop and manufacture vaccines using platform technologies. Moderna, Emergex, and Codagenix are just a few startups that are attempting to leverage platform technologies in response to COVID-19.

Because the technologies underlying vaccine platforms are relatively new compared to traditional vaccine development methods, many of the products made with vaccine platform technologies are still in the research and development phase and comparatively few have actually made it to market. Notably, no nucleic acid vaccines are currently on the market. The platform vaccines that are currently available include, but are not limited to, those listed in Table 1 below.

27 Rajão, Daniela, S. and Pèrez, Daniel, R. "Universal Vaccines and Universal Platforms to Protect against Influenza Viruses in Humans and Agriculture." Frontiers in Microbiology, 2018. Available Online. https://www.frontiersin.org/articles/10.3389/fmicb.2018.00123/full

28 Technavio Blog. "Top 10Vaccine Manufacturers in the World 2020." April 12, 2020. https://blog.technavio.com/blog/top-10-vaccine-manufacturers

29 AstraZeneca. "AstraZeneca to supply Europe with up to 400 million doses of Oxford University's vaccine at no profit." June 13,2020. https://www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-to-supply-europe-with-up-to-400-million-doses-of-oxford-universitys-vaccine-at-no-profit.html

30 CSL. Queensland University's COVID 10 Vaccine to Commence Human Trials. July 13, 2020. https://www.csl.com/news/2020/2020713-queensland-university-covid-19-vaccine-to-commence-human-trials

Table 1: Product Map of Platform Vaccines

Product	Platform	Intended Use	Availability in US	Source
Dengvaxia	Viral Vector	Dengue	Only for those living in an affected area	Sanofi Pasteur
Imojev	Viral Vector	Japanese encephalitis	No	Sanofi Pasteur
Stamaril	Viral Vector	Yellow Fever	Yes	Sanofi Pasteur
Ervebo	Viral Vector	Ebola	Yes	Merck
Zabdeno/ Mvabea	Viral Vector	Ebola	Yes	Johnson & Johnson
FE-LV	Viral Vector	Feline leukemia	Yes	Merial
Provenge	Expression System-Baculovirus	Prostate cancer immunotherapy	Yes	Dendreon Pharmaceuticals
Ceravix	Expression System-Baculovirus	HPV	Yes	GSK
FluBlok	Expression System-Baculovirus	Influenza	Yes	Sanofi Pasteur
Gardasil	Expression System-Yeast	HPV	Yes	Merck
Recombivax	Expression System-Yeast	Hepatitis B	Yes	Merck
Engerix-B	Expression System-Yeast	Hepatitis B	Yes	GSK

The number of platform vaccines on the market will expand as some of those currently in pre-clinical or clinical trials receive FDA approval and as novel vaccines and platforms are developed. There are numerous platform vaccines currently being tested for a variety of uses, including the treatment of COVID-19. COVID-19 vaccine candidates span the spectrum of platforms, and include vaccines made with mRNA, DNA, viral vectors, expression systems, and novel platforms. In addition, some of the platforms being tested for use in a COVID-19 vaccine have or are currently being tested for the treatment of non-coronavirus diseases such as HIV, Influenza, Zika, Sars, Ebola, HPV, cancer, etc.

Current Governance and Regulation

U.S. Federal Legislation

There is no U.S. federal legislation that is specific to vaccine platforms, but there are a number of laws that are applicable in various ways.

- **Public Health Service Act.** Defines biological products, and sets guidelines for their regulation and licensure, including the regulation of GMOs.[31] [32] Platform-based vaccines are defined as biological products and are subject to the guidelines stipulated in the Act. Those using genetic recombinant technologies, such as recombinant viral vectors, are classified as GMOs and subject to the additional GMO regulations.

- **National Childhood Vaccine Injury Act of 1986.** Established national vaccine program and national vaccine injury compensation program. The Act also states that vaccine manufacturers are not liable for side-effects.[33] This is particularly relevant for platform vaccines in which side-effects may be rare or unexpected due to the novel nature of the technologies.

- **Federal Food, Drug, and Cosmetic Act.** Establishes best manufacturing practices for finished pharmaceuticals, including opportunities for accelerated licensure in cases of emergency. This could contribute to the potential use of streamlined regulatory processes for vaccines that utilize existing platforms. The Act also provides guidelines for the regulation of GMOs. [34]

- **Coordinated framework for the Regulation of Biotechnology.** Establishes basic federal policies for the development of products created with biotechnology, such as GMOs and other synthetic biology products. [35] Vaccines using platform technologies are created using biotechnology and are therefore subject to the regulations in the framework. For example, nucleic acid vaccines are considered synthetic biology products and recombinant viral vector vaccines are GMOs.

- **FDA Amendments Act of 2007.** Expands clinical trial bank and mandates that a certification ac-

31 Title 42 USC, Chapter 6A Public Health Service, Subchapter II General Powers and Duties, Part F: Licensing of Biological Products and CLinical Laboratories, Subpart 1- biological products, Section 262: Regulation of Biological Products. Available Online. https://uscode.house.gov/view.xhtml?req=(title:42%20section:262%20edition:prelim)

32 Title 42 USC, Chapter 6A Public Health Service, Subchapter XIX Vaccines. Available Online. https://uscode.house.gov/view.xhtml?path=/prelim@title42/chapter6A/subchapter19&edition=prelim

33 H.R. 5546 National Childhood Vaccine Injury Act of 1986. Available Online. https://www.congress.gov/bill/99th-congress/house-bill/5546

34 Title 21 Food and Drug CFR, Chapter 1 Food and Drug Administration Department of Health and Human Services, Subchapter C: Drugs: General, Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals. Available Online. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

35 Library of Congress. " Restrictions on Genetically Modified Organisms: United States." https://www.loc.gov/law/help/restrictions-on-gmos/usa.php

company a product submission to the FDA [36] Like all vaccines, platform vaccines must obtain FDA approval, and are subject to the guidelines set forth in the Act.

U.S. Governance Frameworks

- **USDA Veterinary Services Memorandum.** Provides licensing guidelines for non-viable, non-replicating vaccines using platforms. The guidelines allow streamlined regulatory processes for products that utilize existing platforms.[37]

- **FDA Guidelines.** The Center for Biologics Evaluation and Research at the FDA is the regulatory body that governs vaccine testing and approval for humans.[38]There are various FDA guidelines and memoranda that are applicable to vaccine platforms. They cover topics such as manufacturing, clinical and non-clinical features, and licensure. Some examples include, but are not limited to:

- FDA "Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications"[39]

    - FDA "Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Being Used in the Production of Viral Vaccines for Infectious Disease Indications" [40]

    - FDA "Guidance for Industry: Data Needed to Support the Licensure of Pandemic Influenza Vaccines"[41]

International Regulation

Different countries have their own laws regarding the production and use of vaccines, the development of biological products, and the regulation of GMOs. They also have their own national regulatory authorities (NRAs) that control the production of vaccines and other pharmaceuticals.

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36 Food and Drug Administration. "Food and Drug Administration Amendments Act (FDAAA) of 2007." March 29, 2018. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-amendments-act-fdaaa-2007

37 Shere, Jack, A. "Veterinary Services Memorandum 800.213." United States Department of Agriculture, 2015. Available Online. https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_213.pdf

38 Centers for Disease Control and Prevention. "Vaccine Testing and the Approval Process." May 1, 2014. https://www.cdc.gov/vaccines/basics/test-approve.html#:~:text=Vaccine%20Product%20Approval%20Process,-Journey%20of%20a&text=The%20U.S.%20Food%20and%20Drug,vaccines%20in%20the%20United%20States.&text=After%20approving%20a%20vaccine%2C%20FDA,production%20to%20ensure%20continuing%20safety.

39 US Department of Health and Human Services: Food and Drug Administration. "Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications." November, 2007. Available Online. https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--Considerations-for-Plasmid-DNA-Vaccines-for-Infectious-Disease-Indications.pdf

40 US Department of Health and Human Services: Food and Drug Administration. "Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications." February, 2010. Available Online. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/characterization-and-qualification-cell-substrates-and-other-biological-materials-used-production

41 US Department of Health and Human Services: Food and Drug Administration. "Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines." May, 2007. Available Online. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-data-needed-support-licensure-pandemic-influenza-vaccines

- **WHO Guidelines.** There are various WHO guidelines and memoranda that are applicable to the use of vaccine platforms in member countries. They cover topics such as manufacturing, clinical and non-clinical features, and licensure. Some examples include, but are not limited to:

- WHO "Guidelines for ensuring the quality and non-clinical safety of DNA vaccines"[42]

  - WHO "Guidelines on the quality, safety, and efficacy of Ebola vaccines"[43]

  - WHO "Guidelines on nonclinical evaluation of vaccines"[44]

  - **European Medicines Agency Guidelines on live, recombinant viral vaccines.** Provides guidance to European Union countries on quality, and clinical and non-clinical aspects of viral vector vaccines.[45]

- **Developing Countries Vaccine Regulators Network (DCVRN).** The DCVRN was developed by the WHO to discuss regulatory issues and help strengthen NRAs by providing a space to share information and advice surrounding clinical trials.[46]

Public Policy Considerations

Public purpose issue relating to vaccine platforms include:

- **Regulation.** Since vaccine platforms are designed to be "plug-and-play," some experts argue that regulatory approval should only be needed once. After a platform technology has been approved, it can be used in novel vaccines without needing to be reapproved each time. This would facilitate our ability to respond swiftly to emerging diseases, which is especially important when a disease has epidemic or pandemic potential. However, it would also bypass safety and efficacy studies that ensure vaccines are well-tolerated and provide disease protection. Because vaccines are administered to healthy people, very few side-effects are permissible and the testing and regulatory processes have

42 World Health Organization. " Guidelines for assessing the quality and nonclinical safety evaluation of DNA vaccines." 2007. Available Online. https://www.who.int/biologicals/publications/trs/areas/vaccines/dna/Annex%201_DNA%20vaccines.pdf

43 World Health Organization. " Guidelines on the quality, safety and efficacy of Ebola vaccines." 2018. Available Online. https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_TRS_1011_web-2.pdf?ua=1

44 World Health Organization. " WHO guidelines on nonclinical evaluation of vaccines." 2005. Available Online, https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

45 European Medicines Agency. "Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines. 2010. Available Online. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-live-recombinant-viral-vectored-vaccines_en.pdf

46 World Health Organization. "Developing Country Vaccine Regulators' Network." May 30, 2012. https://www.who.int/immunization_standards/vaccine_regulation/dcvrn/en/

to be extremely strict. There is also no guarantee that a particular platform will work for a particular vaccine, regardless of its use in other vaccines. If a regulatory process moves too quickly and is unable to adequately evaluate the efficacy and safety of a vaccine, an ineffective or dangerous product could be widely distributed. The need to respond to new diseases quickly must be balanced with the need to ensure the safety and well-being of the recipients.

- **Public Health.** Vaccines platforms aid in the development of vaccines to stop the spread of diseases that have epidemic or pandemic potential and therefore pose a significant threat to public health. In addition, vaccine platforms can potentially be used to address other widespread public health issues such as cancer or diabetes. However, as with any vaccine products, vaccines using platform technologies carry the risk of rare or unknown side-effects. For example, although DNA vaccines have been demonstrated to be very safe in clinical trials, there are concerns about potential chromosomal integration leading to gene mutations, or the spread of antibiotic resistant genes.[47] Similarly, viral vector vaccines that are replication-competent carry the risk of pathogenesis.[48] These concerns about unintended consequences are particularly salient since platform technologies are fairly new and our experience with their long-term effects is limited.

- **Marketing.** Vaccine platforms garner significant attention from investors and policymakers because they are novel and have the potential to significantly reduce vaccine development timelines and improve responses to emerging diseases. This publicity is important for manufacturers to gain the capital and resources required to produce a new vaccine. Therefore, the use of "platform" as a buzzword drives innovation and research by increasing interest. However, there is motivation for vaccine manufacturers to label their products as platforms in order to improve marketing opportunities, regardless of whether they are true platforms or not. [49] This could lead to unrealistic expectations about the product's ability to facilitate or speed up a public health response.

- **Access.** Vaccine platforms have the potential to help streamline the vaccine manufacturing process, allowing them to be produced more quickly and in greater quantities. Greater quantities could yield greater access. This is particularly important in developing countries that frequently deal with disease outbreaks and in pandemic situations. Platform technologies also facilitate the development of stockpiles for future use. However, there is concern that new vaccines will be subject to exorbitant pricing that will reduce access to treatment, particularly in developing countries and lower socioeconomic

47 Stenler, Sofia, et al. "Safety and efficacy of DNA vaccines." Human Vaccines & Immunotherapies, 2014. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896608/#:~:text=Among%20the%20risks%20that%20WHO,spreading%20of%20antibiotics%20resistance%20genes.

48 Choi, Youngjoo and Chang, Jun. "Viral vectors for vaccine applications." Clinical and Experimental Vaccine Research, 2013. Available Online. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3710930/

49 Adalja, Amesh, A., et al. "Vaccine Platforms: State of the Field and Looming Challenges." Johns Hopkins Bloomberg School of Public Health: Center for Health Security, 2010. Available Online. https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf

populations within countries.[50] In addition, traditional vaccine technologies that remain important for combating disease may have to compete with vaccine platforms for resources and funding. There is a risk that increasing access to one treatment for one disease could result in a lack of access to treatment for another disease.

- **Biosafety/Environment.** Vaccine platforms that require the use of genetic engineering and recombinant technology fall into the category of genetically modified organisms (GMOs). These GMOs could pose an environmental or biosafety risk. This is of particular concern for viral vector vaccines that may undergo accidental virulence changes such as recombination with wild-type viruses. [51]

- **Consumer Trust and Misinformation.** "Vaccine hesitancy," as defined by the WHO, is a trend in which personal and/or religious beliefs result in fears about vaccination. Myths surrounding the safety and efficacy of vaccines, such as the erroneous belief that they cause autism or neurological damage in children contribute to this phenomenon. Misinformation about vaccines has resulted in a widespread anti-vax movement that has caused outbreaks of diseases previously thought to be eradicated, such as measles in the United States. [52] With the novelty of vaccine platforms, there will inevitably be increased concerns about safety. Without proper transparency and adequate communication of information regarding risks and side-effects, platform technologies could increase the prevalence of misinformation and fuel the anti-vax movement.

50 Sherrell, Zia. "Experts weigh in on how much a dose of a successful coronavirus vaccine could cost." Business Insider, 2020. https://www.businessinsider.com/how-much-will-coronavirus-vaccine-cost-2020-5

51 Aline, Baldo, et al. "General Considerations of the Biosafety of Virus-derived Vectors Used in Gene Therapy and Vaccination." Available Online. Current Gene Therapy, 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905712/

52 Galway, Mirren. "Anti-Vaxxers: A Threat to Our Future." Journal of Public Health Management and Practice, 2019. Available Online. https://jphmpdirect.com/2019/08/23/anti-vaxxers-mirren-galway/

Appendix:
Key Questions for Policymakers

Classification/Taxonomy

- Should vaccine platform technology be defined in the law? What should be allowed to qualify as a true platform?
- How should research and development resources be allocated among platforms? Between platforms and traditional vaccine technologies? Where should funding sources come from?

Regulation

- Should there be a standardized Investigational New Drug (IND) application process for specific platforms?
- If regulatory processes are streamlined, under what conditions should that occur? How many products must successfully use a platform before it can be pre-approved?
- Should there be different regulatory processes for different platforms?
- Should there be exceptions that allow certain regulatory guidelines to be bypassed in an emergency situation such as a pandemic?

Access

- Does the government have a role in regulating the way manufacturers price vaccines and/or in prohibiting exorbitant vaccine prices?
- How can we ensure that increasing funding and resources for platform vaccines does not limit access to other vaccines and treatment methods?
- What role should the US play in using vaccine platform technology to ensure global access to vaccines?

Vaccine Development/Marketing

- How can the pluripotency of vaccine platform technologies help to alleviate the risks of market uncertainty? Can this be used to expand the US domestic vaccine and pharmaceutical markets?
- Should the idea of platform technology be used as a marketing tool by vaccine developers?

- Under what circumstances should intellectual property laws apply? Under what circumstances should platform technology be shared with other companies or other countries?
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Public Health

- Should vaccine manufacturers be responsible for side-effects associated with platform vaccines?
- How can we balance the need to expedite the vaccine development process with the need to mitigate risks?
- What role should the government play in combating misinformation and vaccine hesitation surrounding new platforms?
- How should the government regulate potentially unethical uses of the technologies used in developing vaccine platforms, such as gene therapy?
- What public health concerns should be prioritized for treatment using vaccine platforms?
- How can the US use vaccine platform technology to expand its leadership role in global public health?

Genetically Modified Organisms

- Is there sufficient GMO regulation to account for increasing use of recombinant products in vaccines?
- Should consumers be made explicitly aware when vaccines contain GMOs? How much information should they be provided about the GMOs contained in vaccines?