Planning Ahead for Access to Medicines: Strategy to Integrate Access as a Core Driver of a Vaccines Company

PLANNING AHEAD FOR ACCESS TO MEDICINES: STRATEGY TO INTEGRATE ACCESS AS A CORE DRIVER OF A VACCINES COMPANY

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Abstract

Pharmaceutical companies are investing a considerable amount of effort and resources into access to medicines–related initiatives. However, the manner in which access to medicines is framed and understood may differ between companies, as may its outcomes. This project is based on the idea that access to medicines programs need to evolve towards a more integrated approach that implies incorporating access provisions in the early stages of product development.

By analyzing how Takeda Pharma conceptualizes and operationalizes access, this study aims to develop an adequate access strategy for its vaccines unit. To that end, a series of interviews with employees and external experts on vaccines and access have been conducted. Documentation analysis has also been performed: review of internal data on processes together with the access-related information generated by the company, as well as the outcome of the biannual Access to Medicines Index report.

The outcome of this initial research phase opens the door to the definition of a strategy for Takeda Vaccines that aims at integrating access concepts into the different stages of product development with the objective of strengthening its approach to access to medicines. This strategy needs to be adapted to the specificity of the company; therefore, it is important to understand not only its standard operating procedures and internal organization, but also how its culture and vision integrate and align with access concepts.

This research proposes incremental changes in existing procedures and systems that will lead to structural changes in the way in which the company manages access to vaccines. This implementation will potentially induce a cultural change in the organization that will culminate in the embodiment of access as a core part of the business model of Takeda Vaccines.

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1 INTRODUCTION

Access to medicines (ATM) is not a new concept; it has existed for decades (Vagelos, 1991), and although its approach has evolved from a donation-based perspective to a more contemporary one that aims for sustainability, outcomes are still far from ideal (Rockers et al., 2017) .

ATM is attracting a considerable amount of attention from the pharmaceutical industry. The reason could be a genuine interest in creating products available to as many people as possible, including those who cannot obtain them. However, there is also a strong interest in improving government, stakeholder, and consumer perception and trust in pharma.

Besides pharma's growing interest and efforts towards the development of stronger and more effective ATM initiatives, strategies, or campaigns, it is probably in the vaccines area where more interesting challenges arise, simply because vaccines are strongly linked to access.

Vaccines are a very effective public health intervention tool; in fact, in some countries, they are considered "cornerstones of public health services" (Andre et al., 2008). They are normally delivered through large-scale immunization programs that aim to reach a considerable part of the population (children, in most of the cases), leading to reduced morbidity and mortality. Also, although they may go unnoticed, vaccines play an important role in reducing inequities, as shown with the impact of the introduction of Prevnar (Figure 1) (Flannery et al., 2004).

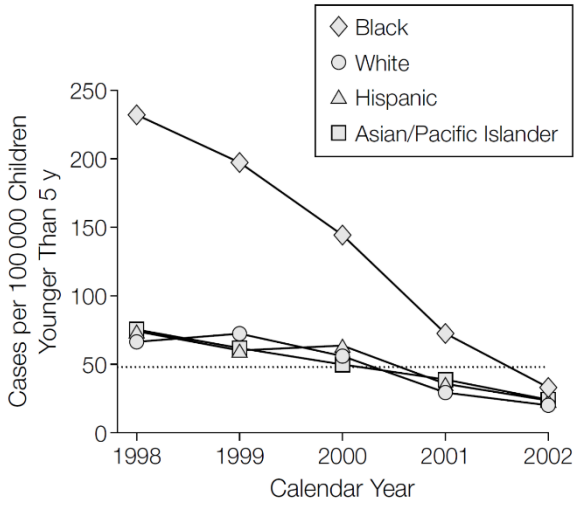

Figure 1: Incidence of invasive pneumococcal disease among children younger than 5 years, by race and ethnicity, in the active bacterial core surveillance system, 1998–2002. Source: Flannery et al., 2004.

However, the increasing numbers of vaccines recommended by the World Health Organization's (WHO) Expanded Programme on Immunization (EPI) is packing national immunization schedules with vaccines,

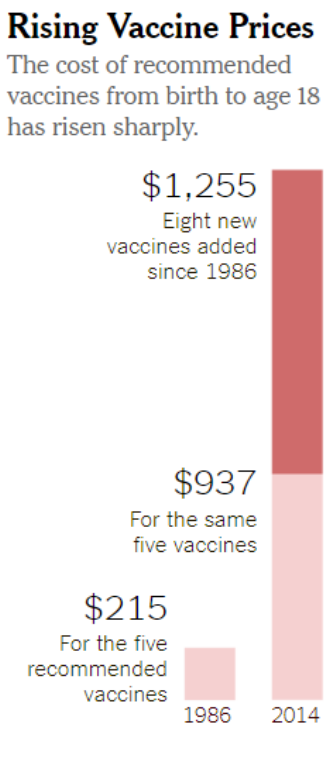

Figure 2: Number of vaccines recommended per child and cost increase in the last three decades in the US. Source: The New York Times, 2014.

which together with the rise in cost of the products (Figure 2) (Rosenthal, 2014), is generating a difficult situation for some governments (Shen et al., 2014). The challenge is not only financially linked to the purchase of the vaccines, it also imposes a huge burden related to the logistical challenges associated with vaccine storage and delivery.

The development of global initiatives such as the Global Alliance for Vaccine Immunization (GAVI) has helped the international community achieve immunization targets. GAVI, the paradigm of large-scale and successful access initiative, has been paramount, during almost two decades, in enabling vaccine delivery to the low- and middle-income countries (LMIC). Besides its notable virtues, this initiative has also some flaws: the challenges for countries that are transitioning out of the scope of the program (Saxenian et al., 2015), the fact that only a few vaccines qualify for funding, potential conflict of interest at board level (Berman and Malpani, 2011), as well as the GAVI bidding system, which drives vaccine prices down to sometimes unsustainable levels for vaccine companies, occasionally rendering it less attractive from a research and development (R&D) perspective.

The regulatory environments of different countries also pose challenges to vaccine companies. The burden of dealing with myriad national regulatory authorities and different requirements adds complexity to an already costly process and hinders the availability of vaccines in some markets (Pezzola and Sweet, 2016).

Moreover, past examples of poor global coordination for epidemics response such as H5N1 influenza (Lee and Kamradt-Scott, 2011) demonstrate the lack of international cooperation in vaccines management.

The fact that there is only one agreed framework for vaccine availability worldwide in the event of an outbreak (i.e., the Pandemic Influenza Preparedness [PIP] Framework) (WHO, 2018) reveals the complexity of establishing international mechanisms for guaranteeing vaccine access for populations in need.

These examples showcase the complexity of the global vaccines environment. Therefore, as mechanisms at a global level are not ideal, and cooperation among actors is weak, to say the least, one of the answers to access can probably be found within the vaccines companies themselves.

However, although companies have shown some progress in their approach and impact on ATM during the last decade[*], good practices still appear "limited to a narrow range of products and countries"(Access to Medicine Foundation, 2016). This project aims to address this limited vision and approach to access by developing a strategy to enable a cultural change that will incorporate access as part of the core business of the company. Ideally, this approach will, with time, generate best practices throughout the vaccine value chain.

[*] According to evaluations by the Access to Medicine Foundation during the last 10 years.

2 ANALYTICAL PLATFORM

2.1 STUDY RATIONALE

Access to medicines (ATM) is an essential element of universal health coverage. Pharmaceutical industry has been involved in facilitating access to medical technologies for years. However, and despite the interest in developing coherent, sustainable, and well-crafted ATM initiatives (either legitimate or led by market pressure within the corporate value programs of the company), the sophistication or success of its implementation has been very limited (Rockers et al., 2017). In most cases, as Rockers et al. show, pharma translates ATM into either product donation or price reduction. This approach to ATM offers a very limited vision of what access means, considering access mostly as the last step in the chain: Only once is the product available do companies proceed to develop programs that will hopefully reach those who need them but who, for some reason, cannot obtain them.

Framing is critical. Understanding access through this limited perspective will narrow the scope of initiatives. This narrow approach is probably the reason drug donation has been for many years a preferred initiative among companies willing to engage in ATM. Past experience, on the other hand, shows that this is not always the best option; there are multiple examples of drug donations that have failed[*] (Clark and Embrey, 2012) or even concerns on how donations can destabilize normal market dynamics (Baker and Ombaka, 2009).

As Bigdeli et al. (2013) show in their research on health systems, "Access to Medicines is addressed mainly through fragmented, often vertical approaches usually focusing on supply, unrelated to the wider issues

[*] Different causes can lead to failed drug donation initiatives; some of them are: relevance of the drugs to the market, local capacity to deliver drugs, national registration and compliance, labeling, expiration, and costs of disposing unusable donations (Mistry, 2017).

of access to health services and interventions" (Bigdeli et al., 2013). Several frameworks do take into consideration a wide range of barriers to access that expand the concepts of ATM being supply-focused[*]. However, it is unclear to what extent these frameworks are implemented in the design of initiatives, as evaluations of pharma's ATM strategies are not common practice (Rockers et al., 2017).

That said, the need for a different role for pharma in health is patent; leading voices in global health appealing for private sector engagement in public health are not an oddity, e.g., Dagfinn Høybråten, the former chair of the Global Alliance for Vaccine Immunization (GAVI) board, or Peter Sands, the executive director of The Global Fund (Hoybraten, 2014; Sands, 2019).

Some steps in the right direction have been made during the last decade. Initiatives have been developed (GHIT [Global Health Innovative Technology Fund], Access Accelerated, CEPI [Coalition for Epidemic Preparedness Innovations]) aiming to create sustainable partnerships between the public sector and the pharmaceutical industry, and forums have been created to address the need for pharma to ensure more effective and equitable innovation, access, and delivery of health technologies (Moon, 2019).

The global community is appealing to pharma to consider ATM a part of their core mission and not as a simple "extra" activity that needs to be performed. Furthermore, if pressure from the societal and global health community continues to increase in the years to come, it is probably only a matter of time before global pharmaceutical companies initiate the transition to this new mindset.

[*] Based on the analysis by Bigdeli et al. (2013): WHO–MSH (Management Sciences for Health) 2000 framework, WHO 2004 framework, and Frost and Reich 2010 framework.

2.2 ACCESS TO MEDICINES VS. ACCESS TO VACCINES: FRAMEWORKS

Although access to vaccines (ATV)* initiatives are embedded by default within ATM activities**, the vaccine market operates under a different set of rules from the pharma non-vaccine products market*** (see Appendix 9.1). Vaccines are different products that involve a different set of actors, safety concerns, risk considerations, and target populations. This specificity could open the door to challenging the validity of the mentioned ATM frameworks. However, Frost and Reich have demonstrated the successful application of their proposed framework for vaccine products and technologies (Frost and Reich, 2009a).

On the other hand, there have been recent efforts to develop a specific access framework for vaccines. Due to the mentioned specificity of the vaccine business, the Access to Medicine Foundation (ATMF) has developed an ATV Index. This Index uses a new framework (see Appendix 9.2) to measure and compare access capacities among vaccine companies by evaluating three key domains: research and development (R&D) (investments, number of vaccine projects, technological development projects, number of access provisions in place), affordability (pricing strategy, transparency, registration), and manufacturing and supply (overcoming local barriers, ensuring rational use, responding to shortages, aligning supply and demand, supporting vaccine security, increasing global manufacturing capacity) (Access to Medicine Foundation, 2015). The Index results do not show best practices, only a ranking of companies based on their accomplishments (how they are aligned to their framework's indicators). However, best practices can be distilled from information shared in their documents.

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* Although ATV is the more accurate term to refer to access strategies within a vaccine company, throughout the document the terminology used is ATM since is the most widely accepted way to refer to access.

** Usually part of the companies' ATM chapter of CSR (corporate social responsibility) reports.

*** Vaccines are in general administered and distributed by governments through national immunization programs. The presence of the private sector is limited.

ATMF's frameworks open the door to a new approach to developing ATV strategies, bringing an access perspective to product development and indicating a set of factors a company can develop to improve access to its products. It can be argued that this approach is somehow limited, as its focus appears closer to the business development side, and does not take into consideration other external stakeholders, political interests, social values, and market dynamics that also affect access as other frameworks do (Frost and Reich, 2009b). However, ATMF's perspective is aligned more to the objectives of the present research project, as it helps to identify the processes pharma needs to work on to improve the availability of the right product in the targeted market. In the second phase, once these internal gaps have been addressed, it will be the time to implement those other frameworks to improve product accessibility.

This may be a new approach to access but it is already garnering some interest. The ATMF itself also states the importance of embedding an ATM strategy in the product development phase. It raised the following question: "Is it time for access planning to become a standard practice during product development?" (Access to Medicine Foundation, 2017). To that end, they have added a new indicator that measures access provisions in the early stages of product development. This will potentially define a shift in the integration of access in the pharma and vaccine industry, and this project aims to establish the grounds for Takeda Pharma to be one of the leading companies of this trend.

2.3 RESEARCH PROJECT OBJECTIVE

Takeda Pharma is attempting to become one of the top global pharmaceutical actors[*]; for around 200 years, the company has focused its operations in the Japanese local market, and only during the last

[*] The company has been growing during the last decades through a set of international acquisitions. Despite this, its 2018 USD 12.54B revenue (BioSpace, 2019) is far from that of the top 10 players in the pharma industry (Ellis, 2019). In the coming months, once its acquisition of Shire has been accounted for, Takeda's position in the ranking is expected to change considerably.

decades has it begun its expansion out of Japan. This move has also been followed by a growing interest in being considered a more prominent actor in ATM. Takeda's Vaccine Business Unit (VBU) needs to step up to the challenge. However, this relatively new unit does not have a clearly defined strategy for ATV.

Although the final objective of this project is to increase Takeda Vaccines' ATM impact, the true focus of the present research is to develop a strategy that will lead to initiatives that will create an ATM-friendly environment. The purpose of this project is not to define what access initiatives to launch, but to develop a culture that will lead to the generation of access initiatives that are adequate[*].

To address this issue, the research project is framed as follows:

How does Takeda Pharma conceptualize ATM, how does its vaccines unit operationalize it, and how can it be improved?

This question implies different research stages that build on each other:

- Analysis of what ATM means for Takeda
- Evaluate how this concept is translated into Takeda Vaccines' product development process
- Adapt existing strategies and protocols or develop new ones to facilitate this implementation

The project involves the following stages: research analysis, strategy development, initiatives proposal, and implementation.

[*] Adequate not only in terms of high impact for the right population, but also from the organization's perspective. Initiatives that align with the company's vision and that can be implemented in a manner that will not be challenged by every operational change in the organization.

2.4 METHODS

For the data gathering phase that aims to understand trends in access, Takeda's approach to access, and Takeda's manner of working, the following information sources were used: Literature review, interviews with Takeda employees and external experts on access, review of Takeda's internal strategy on access as well as processes and documents used throughout the vaccine value chain, and analysis of the ATMF Index submission and results.

The main characteristics that define each data source are described in the following sections. The findings will be described in the following chapters.

2.4.1 LITERATURE REVIEW

The literature review focuses on two areas. The first area involves understanding ATM and ATV. Second, understanding how a new strategy and activities can be integrated into an organization. The latter is not highly critical for the scope of the project but will help in defining the right strategy and steps to be followed.

There is substantial ATM-related literature. The search term "access to medicines" returned more than 600 articles in the PubMed database, more restricted than the 28,000 results returned in Google Scholar. Common topics discussed are examples of access initiatives, frameworks on access, or financial and commercial challenges for pharma, to mention just a few.

When narrowing the research scope to vaccines ("Access to vaccines"), the results were more limited: 97 in PubMed and around 3,700 in Google Scholar. Some examples refer to global action to fight diseases such as influenza, the need for partnerships, and inequities and financing strategies. In general, they address downstream issues related to program implementation (or the need for access programs). Nevertheless, this does not address the present research concerns.

Following a more targeted search (“access to vaccines” AND “value chain”), PubMed did not yield any results and Google Scholar returned only 95 results. Some articles mention the need to adapt product development to address the needs of the targeted population with the objective of improving treatment availability and affordability (So and Ruiz-Esparza, 2012). Others steer attention to the importance of investing in technology transfer through the development of manufacturing facilities in the low- and middle-income countries (LMIC) (Hendriks et al., 2011) (WHO, 2012a). And others, argue about the critical importance of a well-adapted research and development strategy for drugs aimed to LMIC (Chaumont, 2018). However, the majority of the literature ignores the importance of addressing access in the early stages of vaccine development.

Due to this lack of success, the next step involved using even more specific search terms. At this stage, the search was focused on finding articles linking ATM to the early stages of product development. However, the search terms (“access to vaccines” AND “value chain” AND “cultural change”), (“access to vaccines” AND “R&D” AND “early stages” OR “Cultural”), (“Access to vaccines” AND “organizational change” AND “R&D” OR “early stages”) also did not generate interesting results.

Despite this failure to find articles through systematic literature review, some valuable information was nevertheless obtained from the grey literature as well as the Takeda internal database.

The second part of the literature research is also relevant to this project: To identify the techniques to adopt for integrating an access strategy into the core of the company.

To that end, there is a need to widen the scope of the research to organizational change literature, which is not necessarily linked strictly to ATM.

In this case, the search performed for pharma and organizational change did not yield valuable data. However, attempting a different approach led to some progress (“CSR” AND “integration” AND “core”). It

is possible to find works that analyze the steps and impact of the integration of corporate social responsibility (CSR) activities into the core functioning of a company.

Although it is expressed in the chapter 6 in this document that ATM and CSR activities should not be considered equivalent, it may be argued that this does not preclude comparing how they integrate into the core business of a company. The reason is that, although ATM and CSR should be treated differently conceptually, operationally they share important traits that make them comparable.

2.4.2 INTERVIEWS

Interviews are a critical means of obtaining information on the manner in which the organization operates. The interviews focused on processes and access-related activities. The objective was to determine the access strategies being implemented, what (if any) standard operating procedures (SOPs) are being followed, and in general, the tools and frameworks Takeda uses to develop access strategies, how they measure them, as well as indicators and objectives.

It was also important to understand the connection between the main global ATM office and the VBU. That is, how is this link established and what are the implications in the development of initiatives.

Lastly, it was also crucial to determine how access is understood within the different levels of the vaccine development process, and how the message from leadership on access percolates and is translated into policies or initiatives.

To achieve these objectives, the interviews followed a structured approach through a questionnaire (see Appendix 9.5 for the questions). As the interviewees had different levels of competence and responsibility, some questions may not have been pertinent to all of them. Nevertheless, this was taken into consideration and adapted during the interviews.

The questions were purely operational; the focus of the interviews was not the employees, but the processes involved in their daily tasks. Takeda permitted the interviews under the condition that they were not recorded. Consequently, this condition pushed the data-gathering process towards an approach based on note-taking and fast transcription after the interview to reduce recall bias.

I conducted more than 30 interviews with Takeda employees, who spanned the entire value chain of the vaccine development process, from discovery to market access, passing through clinical development, medical and policy, operations, regulatory affairs, ethics and compliance, and others. The selection process involved snowballing, starting from leadership downwards.

I had informal interviews with external experts who had been selected based on their current or past roles linked to ATV at a global level. The objective of these conversations differed from that performed within Takeda. Here, it was to understand industry trends, how access is evolving, and their thoughts on vaccine companies willing to adopt a strong ATM approach. There were fewer interviewees because, unlike with Takeda, it would be possible, if needed, to find literature on the topic. Accordingly, the interviewee selection was not focused on numbers, but on areas of expertise: philanthropy (Bill & Melinda Gates Foundation [BMGF]), public–private partnership (GHIT), nonprofit (ATMF, PATH), and academia (Boston University)[*]. Their feedback has been important for understanding potential opportunities in the sector as well as the challenges that access and vaccines may face in the future.

2.4.3 ACCESS TO MEDICINE FOUNDATION INDEX

The ATMF publishes a biannual index (Access to Medicine Foundation, 2018a) that ranks the ATM efforts of 20 of the biggest pharmaceutical companies. The ATMF is a nonprofit organization based in Holland

[*] The private sector is already incorporated through meetings with Takeda Vaccines leadership.

and is supported by the BMGF, the UK Department for International Development (DFID), and the Dutch Ministry of Foreign Affairs.

Their objective is to "stimulate and guide pharmaceutical companies to do more for the people who live in low- and middle-income countries."

To that end, the foundation has developed a framework that has evolved along the years[*] and that has been adapted through feedback from companies and that responds to the new trends in access. This framework, although useful, still has its shortcomings. The ATMF describes its role as defining "action pharmaceutical companies can and should be taking to improve access to medicines in low- and middle-income countries" (Access to Medicine Foundation, 2018b). No consensus defines "what can be done to improve access." The framework is just one tool developed by the ATMF based on its assumptions and analysis, and is not a gold standard approved by the global health community, the World Health Organization (WHO), or multilateral agencies. Therefore, although useful, the results of the Index and the report linked to it are one source of information, but not the answer to solving ATMF's internal problems on the conceptualization and operationalization of access.

Pharmaceutical companies have submitted thousands of pages of documentation, and this information, shared through the biannual report, is an invaluable source of data related to ATM practices. Companies willing to learn about best practices in the industry will gain a good idea of the trends, means of working, and initiatives that have been successful in other companies. Otherwise, considering the Index as an objective in itself, more than a tool, can lead to undesirable outcomes[**].

[*] 2018 is the sixth iteration of the Index.

[**] Focusing on improving the Index results without changing the organization's mindset will probably lead to an ever-changing void scenario, with initiatives linked only to the year's list of indicators. If the indicators change or evolve in a direction that does not align with the core company's values or way of working, the situation would become unsustainable for the company.

The Index ranks pharmaceutical companies according to the following areas: General access to medicine management, Market influence and compliance, R&D, Pricing manufacturing and distribution, Patents and licensing, Capacity building, and Product donations. These areas are then evaluated under four criteria: Innovation, Performance, Transparency, and Commitments. To perform this evaluation, the ATMF has developed a set of almost 70 weighted indicators (see Appendix 9.5).

2.4.4 ANALYSIS OF ACCESS TO MEDICINES AT TAKEDA

Takeda has doubled in size after acquiring Shire, and one consequence is the need for an operational or structural change in some areas. One area affected is the ATM department, as Shire also has an existing ATM department with defined policies and procedures.

Takeda is taking advantage of this transitory period towards the integration to review its policies and approach to ATM. This is therefore an ideal opportunity for Takeda Vaccines to propose changes to its conceptualization and approach to ATM.

The Takeda ATM office is structured in two organizational levels. The head is based in Singapore, overseeing global access and Takeda's vision and guidelines; the second level has different ATM heads for the different business units and departments. The main office does not define the strategy, initiatives, or pathway for each of the different areas in Takeda. Rather, its role is to define corporate vision and the approach to access. Each program area and the business unit should then align with this general vision. The outcome is strong independence among the teams working on access.

2.5 FRAMEWORKS

The ideal outcome of this research project is a framework that encompasses all nuances of the development and implementation of an ATM strategy within a vaccine company. The objective was to find the key path that can be used (and replicated anywhere else) to identify a strategy that could lead to

the development of initiatives on ATM. However, the complexity of the task, which stems from the multiple layers that need to be addressed, opens the door to a different approach that addresses first the identification of the ideal strategy, followed by the development of the strategy, and then its implementation.

As ATM is a topic shared throughout the research and implementation process, the project proposes a set of frameworks that will address the different stages of development, from ideation to implementation. The result, although less compelling than one all-encompassing framework, is a clearer path to a more precise answer to the real core question: What can the VBU do so that it will engage more proactively in ATM?

As mentioned earlier, the project involves different phases: research, strategy development, and proposal and implementation. The following frameworks address the different stages of the project:

- Conceptual
- Analytical
- Strategy development
- Strategy implementation

The first two frameworks will be developed in the following sections, as they are pertinent to the research phase of the study. The subsequent two frameworks will be explained in the development and implementation phases of the report.

2.5.1 CONCEPTUAL FRAMEWORK

The objective of this framework is to define the focus areas that should be considered during the strategy development. After an initial assessment of the company's structure and manner of working, it was possible to identify three areas with a role in the introduction, development, and implementation of

access activities. These areas, shown in Figure 3, are the decision-making actors; the processes and tools used to define objectives; and the access initiatives, strategies, and mechanisms that may already be in place. The objective is to identify the synergies between these three areas that will enable the construction of an environment that will generate an appropriate response to access.

The diagram in Figure 3 depicts how the ATV concept feeds from these three areas. A compelling access strategy that is coherent and adapted to Takeda Vaccines requires partial contributions from each of the areas.

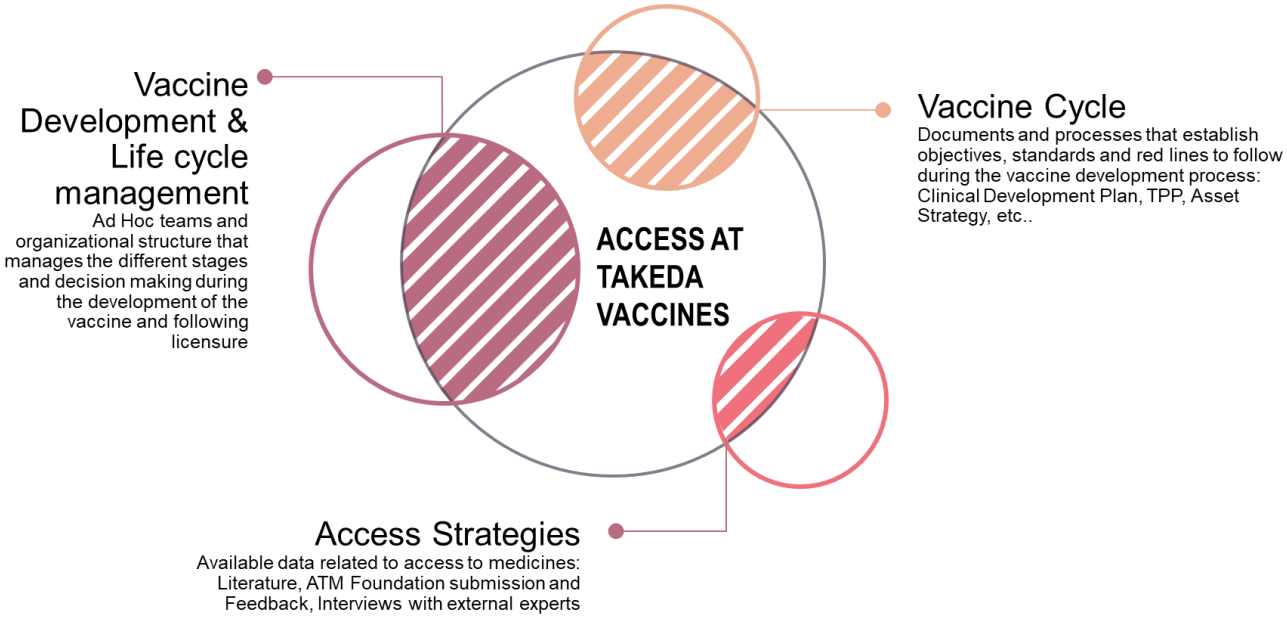

Figure 3: Conceptual framework for defining ATM linkages in a vaccine company. Source: Author's own

2.5.2 ANALYTICAL FRAMEWORK

This framework depicts a very straightforward pathway through the steps followed in the research process, from the literature review and interviews to the final proposal. The steps are, in order: data gathering (Chapter 2), findings (Chapter 3), strategy development (Chapter 4), and proposal (Chapter 5).

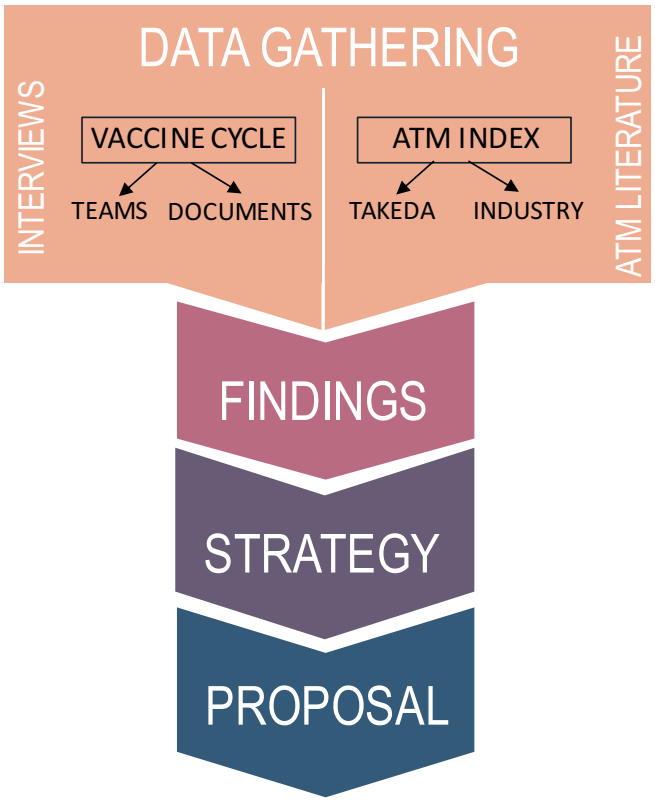

Figure 4. Analytic framework for the research project. Source: Author's own.

3 FINDINGS

This chapter shows the main findings obtained after the data gathering phase. The key takeaway points addressed relate to the following areas:

- Conceptualization of access
- Operationalization of access
- Access to medicines (ATM) activities: Access to Medicine Foundation (ATMF) Index learning points

3.1 TAKEDA'S ACCESS TO MEDICINES CONCEPTUALIZATION

Access is gaining importance in Takeda's operations. In the new Takeda organizational structure (following the integration of Shire), president Christophe Weber stated through an internal announcement the "ambition to deliver sustainable, profitable growth through an innovative portfolio coupled with its Access to Medicines strategy to broaden patient reach."

Takeda's approach to ATM is directed towards the idea of improving health systems performance. Its approach is defined by the following vision:

"We serve the needs of our patients by acting as a catalyst to sustainably strengthen evolving healthcare ecosystems and forging alliances with reputable partners while expanding Access to Medicines impact for our innovative portfolio."

Through this conceptualization, Takeda global ATM has identified four pillars that will, according to the company, help address health systems strengthening through access activities. These pillars are:

- Stakeholder engagement
- Innovative financing
- Capacity building

- Shaping public policy and patient advocacy

Therefore, the activities implemented by the company must be related to these four pillars. This could be challenging, as it may limit the range of initiatives that could be developed. However, it can also be perceived as a push towards a more focused approach that will also generate synergies among the company's business units.

For Takeda Vaccines, the proposed limitation of the scope of access is not a problem so far. The vaccines unit's access initiatives are aligned with and fit the framework. In fact, vaccines unit is leading the way within Takeda in proposing innovative financing strategies, linked to the potential launching of the new dengue vaccine.

Despite the clear mandate of the global Takeda ATM office in terms of approach to access, the situation is constantly evolving. The main office is undergoing a revision of the ATM strategy. This is partially due to the acquisition of Shire[*], but also due to the encouragement received by leadership. As mentioned above, Weber has been a clear proponent of access as the way forward for Takeda Pharma. The ATM Global Office now has the leverage to work towards developing a stronger approach to access.

3.2 TAKEDA'S ACCESS TO MEDICINES IMPLEMENTATION

How does Takeda implement its idea of ATM? The three relevant factors to analyze are: organizational structure, operationalization and activity selection, and development.

3.2.1 ORGANIZATIONAL STRUCTURE

[*] Takeda acquired the pharmaceutical company Shire in January 2019.

Takeda's operational ATM structure is defined by a head office and departments and business units that feed into it through the ATM committees. Theoretically, each head or representative is independent and free to develop the initiatives they consider relevant for their area.

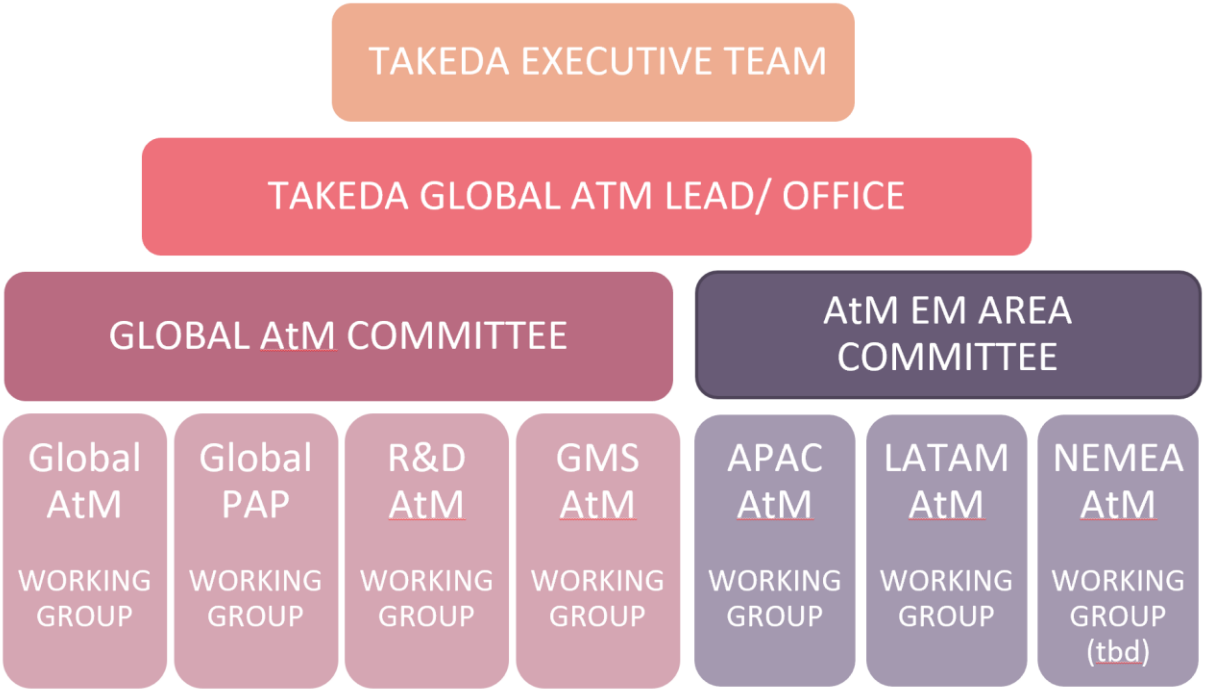

Figure 5: Takeda ATM organizational structure. Source: Takeda ATM Global Office.

Takeda Vaccines does not have a dedicated ATM team. Two people handle all issues related to access: one representative from the Global Medical Team and another from the Market Access Team. They are the appointed Takeda Vaccines representatives in the Takeda ATM working groups and committees. They are also responsible for the biannual data compilation process towards submission to the ATMF. Their involvement in access is just one more task among the list of tasks in their job description. This situation is a handicap not only from the perspective of the workload of those involved, but also in terms of perception. The importance placed on access is also linked to the resources dedicated; in this case, very few. That said, considering the few resources invested in access, the results are remarkable.

The vaccine development cycle means years of work, involves a significant number of people and working groups, and demands innumerable decisions along the way. It seems difficult to identify who decides what or what are the critical decision points that can make a difference. What is clear is that a considerable amount of power is managed by the Global Product Team (GPT), a team formed by representatives from the different functions of the vaccine development process. This team makes decisions and oversees the product development from beginning to end. Another relevant fact is that the human factor plays an important role in the GPT. Relationships among members, as well as individual technical knowledge and skills, are by no means trivial factors that play an important role in the outcome of the GPT's work.

3.2.2 OPERATIONALIZATION

Although there is a Global Access Office, the general idea is that it does not define how the different business units need to develop their initiatives. Each unit is free to manage its access strategy.

The independence granted to each business unit can be perceived as a delegation of responsibilities that would increase flexibility and revitalize the approach to ATM, more tailored to the needs of each department. However, an unwanted consequence is the siloed system, which leads to a lack of transparency, knowledge, or understanding within different areas in Takeda Pharma. The activities and approach to access are not secrets, but a considerable amount of work remains in terms of information sharing among the business areas in the company.

Another downside of this independence might be one reason the vaccines unit does not have an access structure in place: it is a relatively new business unit (eight years old), without products in the market and lacks resources invested in access. Due to this "isolation," Takeda Vaccines will need time to gain a prominent position in access at Takeda.

There is a perception at Takeda that access is somehow present in the decision-making process as part of Takeda's PTRB mantra (Patient-Trust-Reputation-Business, in order of importance) (Takeda, 2014). Contrary to appearances, this could be dangerous. Having Patient as the primary objective, as the core of the corporate values, could be considered a proxy for access. This is not trivial; a misconception of what the company believes vs. what the company does could give the false impression that Takeda is already doing access just because its values are the corporation's keystone and decisions are based on them.

Abstract conceptualizations evoking a patient-centered business is by no means a Takeda idea. It is a common practice in pharma. It will be useful, in this case, to explore how this PTRB framework works and translates into Takeda's decision-making processes. Moreover, the potential integration of an access strategy leveraging this patient-first approach also makes sense.

Although the organization and its employees understand and respect the concept of access, this does not translate directly into their daily tasks or annual objectives. Due to the lack of standard operating procedures (SOPs) on access for the early research and development (R&D) stages, it appears that access is relegated to other teams such as manufacturing, policy, or market access.

Takeda's policies and framing imply that access is taken for granted as a de facto characteristic of Takeda Vaccines. However, it is unclear who carries out access-related activities or what activities are categorized as access activities. Those in the later stages of product development, i.e., manufacturing and commercial, are more aware of the implications of their job on access.

There is a patent siloed mentality among the different teams. A common theme of conflicting interests was raised in several interviews as a potential source of disagreement with overall vaccine achievements. Time to market is a paramount consideration in pharmaceutical companies, and teams under this pressure may lose sight of the overall objective and focus on their own deliverables. This can lead to outcomes that although fulfill the minimum requirements of the product, may have a negative impact on access. A well-

known example is the use of the porcine-derived trypsin instead of recombinant trypsin in cell culture propagation early in the research stage (Grabenstein, 2013). This may impact access among Islamic populations since the product may not get the Halal certification. It would be rare for a scientist working on early development stages and under the pressure of team objectives and deadlines, to consider or even to understand the ramifications of these decisions in terms of access.

Through conversations and meetings with employees, it appears that access is understood as a concept inherent to vaccines; however, it is not reflected in any SOP or any of the documents normally used to define the characteristics of the product whatsoever. Therefore, despite access being "present," it can be easily disregarded as a factor to be considered during decision-making.

3.2.3 ACTIVITY SELECTION AND DEVELOPMENT

Takeda implements an extremely varied range of activities; the common denominator is the main line of action defined by the ATM Global Office. Most of the initiatives fall under stakeholder engagement and in the capacity-building areas (see Appendix 9.2); very few can be found in the innovative financing spectrum, and there is only one initiative in the shaping public policy and patient advocacy realm.

Despite the handicap of not having any product in the market, Takeda Vaccines is also involved in multiple access initiatives (see Appendix 9.3 for a comprehensive list of access initiatives developed by Takeda Vaccines). These initiatives, however, do not follow a predefined access strategy, and many are performed by teams as part of the expected activities of a vaccine value chain process. In general, as mentioned earlier, vaccines are, inherently, access products. Hence Takeda's Vaccine Business Unit (VBU) is doing access just by performing some expected tasks: Applying for World Health Organization (WHO) prequalification or Global Alliance for Vaccine Immunization (GAVI) approval are examples of access

initiatives that are a fundamental part of the vaccine development process for a product that is intended for launch in the low- and middle-income countries (LMIC)[*].

This approach, however, is not structured under the access umbrella, nor is it documented accordingly. If Takeda wants to know what access-related activities are performed within the Vaccines Unit, there is no straight or simple means of finding out. Many activities developed by individuals or teams have not been labeled as access; therefore, tracking them down to identify them becomes an arduous challenge with no guarantee of an accurate result.

The development of access initiatives does not follow a standard procedure, and this could be a consequence of the lack of alignment under a common strategy. Initiatives do not need to follow any standards in reporting, measurement, or evaluation. So, even in the case where access initiatives are identified, evaluating their impact remains extremely difficult. This weakens not only the perception of the individual initiatives but also Takeda Vaccines' overall approach to access.

Teams and individuals have shown interest in pushing access initiatives forward; however, the lack of a defined, VBU-specific strategic approach, the lack of training on available opportunities, as well as the lack of incentives to develop measurement indicators or impact evaluations does not help create a culture that embraces and generates sustainable initiatives.

Leadership, on the other hand, is being very vocal and encouraging pushing teams to think about how vaccines can be made more accessible to more people. That said, this encouragement would benefit from a structure that aids the creation of coherent, sustainable, and measurable initiatives. By not having an access framework in place, the VBU risks developing one-off initiatives that will be difficult to measure or

[*] Takeda Vaccines' pipeline is based on vaccines that will have strong impact in the LMIC: dengue, norovirus, Zika, and polio.

push to their maximum potential, not to mention it could miss the opportunity to scale or replicate successful initiatives in the future, as it is more reliant on people than processes.

3.3 ACCESS TO MEDICINES INDEX RESULTS ANALYSIS

The outcomes of the last iteration of the ATM Index report in October 2018 (Access to Medicine Foundation, 2018a) show some key takeaways that should be considered.

These shared outcomes and ideas are not a set of standards or rules to follow. Instead, they are an analysis conducted by a nonpartisan entity that can aid understanding of the status quo and trends in the ATM field. Due to its financial independence, the ATMF can function as an independent nonprofit organization; hence, it is possible to conclude that its analysis is not biased due to pressure from the market, pharmaceutical industry, or any other stakeholders.

The first takeaway is that, although Takeda is ranked fifth among the 20 evaluated companies, this position will be easily challenged in the next iteration of the Index, as nine companies are grouped very close to each other. However, and more importantly, should Takeda worry at all about its position in the ranking? The evaluation is relative, so it does not reveal as much the company's competence in terms of ATM, asits competence compared to others. In absolute terms, this does not shed much light on how well Takeda is doing in ATM.

Moreover, other interesting conclusions can be distilled from the quantitative analysis of the report shown in Appendix 9.6. Probably the most meaningful is the impact of Takeda Vaccines in relation to Takeda Global in terms of access. It is possible to see how, despite not having marketed products yet, Takeda Vaccines has had an important role in increasing the global overall ATM capacity of the company (according to the index metrics).

In the same analysis, the data also show that the most impactful ATM initiatives according to the ATM framework are those linked to performance and transparency, i.e., mainly the areas of pricing, manufacturing, and distribution, and in R&D. Takeda Vaccines has not had a strong influence in these specific areas, mainly due to a limited pipeline and the nonexistence of marketed products so far, meaning there is considerable room for improvement in the years to come (see Appendix 9.6 for more data).

4 STRATEGY DEVELOPMENT: VISION AND STRATEGIC OBJECTIVES

Once data has been gathered and analyzed, it is time to think about addressing the last part of the proposed question: "what Takeda Vaccines can do to improve its approach to access."

First, an access strategy aligned with the company's way of working and that will address the concerns and opportunities raised during the research phase should be developed, followed by the proposal of actionable initiatives to achieve the desired result.

4.1 STRATEGY DEVELOPMENT FRAMEWORK

The strategy is developed through the PTRB (Patient-Trust-Reputation-Business) Quality Improvement Framework: This conceptual framework shows the steps to follow during the strategy's development process until its evaluation. The concept of PTRB* is critical, as it guarantees that those values are respected during the decision-making process. This framework establishes a coherent pathway from strategy generation to its implementation. It also opens the door to evaluations. An iterative process will allow parameters to be adjusted until the right dynamic that fits Takeda Vaccine's

Figure 6: Strategy development framework: PTRB quality improvement framework for ATM. Source: Author's own.

* PTRB is the set of core values (in this exact order of priority) defined by Takeda Pharma. The background concept is that all decisions are made by evaluating the four parameters, always prioritizing Patient first.

way of working is achieved. This framework will require the development of an impact evaluation. By not doing so, the framework risks failure.

The first stage of the framework is the development of a strategic vision. The subsequent framework depicts how the development of the Takeda Vaccines vision in a structured manner is addressed.

4.2 STRATEGIC VISION DEVELOPMENT

This tool will aid identification of the right strategy by analyzing four pillars: objective, current Takeda Pharma's vision, challenging factors, and levers.

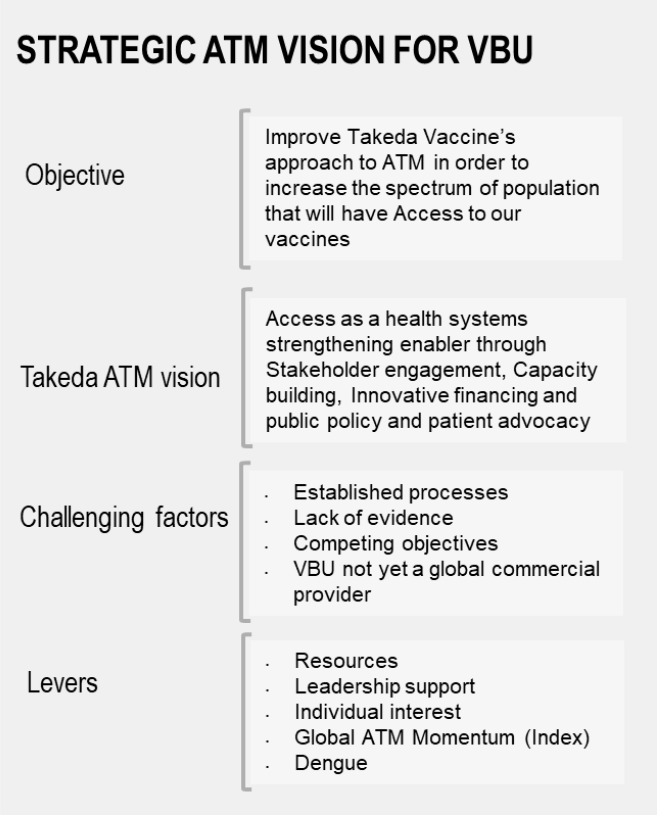

Figure 7: Strategic ATM vision development framework for Takeda Vaccines. Source: Author's own.

This framework is aimed at developing a strategic vision on ATM that will align with Takeda's objectives by taking into consideration the Takeda Vaccines way of working.

To that end, the tool is a variation of a SWOT analysis, where "Strengths" and "Opportunities" are replaced by "levers," and "challenging factors" is used in place of "Weaknesses" and "Threats," complemented by other relevant parameters for this exercise, which are the "vision" of the organization and the general "objective" of Takeda Vaccines:

a) **OBJECTIVE**: To maximize the amount and spectrum of the population reached by Takeda Vaccines through a proactive approach to access to medicines (ATM).

b) **TAKEDA GLOBAL ATM VISION**: Access as an enabler of health system strengthening through stakeholder engagement, capacity building, innovative financing, and public policy and patient advocacy. This vision will be a limiting factor that will determine the scope of the potential initiatives.

c) **CHALLENGING FACTORS:** Aspects that may hinder the application of an ATM strategy. The research phase has led to the identification of four main aspects to consider when developing an access strategy:

- **Established processes:** The company already has a set of procedures that define the steps to follow, and the redlines, measurement tools, and expected outcomes. These processes should be validated by leadership and are not easy to challenge, as most of them are deeply embedded in the vaccines/pharma business. Reaction against changes in these processes should be expected, not only from the leadership, but also from employees, who are used to a certain way of working.
- **Lack of evidence:** As this approach to access in pharma has not been extensively explored before, there are no supporting data for the expected positive impact of a new strategy.
- **Competing objectives:** The final objective of the vaccine company could arguably be to produce the best possible vaccine. However, the definition of "best" is not necessarily linked to access. It will vary based on the team being asked. "Best" may be defined as producing vaccines with the highest possible effectiveness in populations, but it can also refer to the vaccine that brings more benefits to the company, or that is the strongest scientific breakthrough, to mention just a few perspectives.
- **The Vaccine Business Unit (VBU) is not yet a commercial provider outside Japan[*]:** This hinders the possibility of measuring ongoing initiatives that improve access in the low- and middle-income

[*] Takeda does commercialize vaccines in Japan; however, the present project does not consider this stream of the vaccines business for several reasons. The main reason is that the project focuses on improving access to global

countries (LMIC), or proposing new ones. The truth is that a limited spectrum of measurable initiatives can be implemented for early-stage products, and most of Takeda Vaccines' global products are, unfortunately, in those phases. However, there is another, and probably more significant, problem linked to the lack of products in the global market: the impossibility of establishing a baseline and comparing new products and initiatives with existing ones.

d) **LEVERS**: There are, notwithstanding, a set of levers Takeda Vaccines can use to encourage the adoption of a new strategy. Levers identified as critical are as follows:

- **Resources:** Takeda Pharma and Takeda Vaccines, fortunately, have the capacity to invest resources in ideas they consider will bring value to their products. As access is gaining a more prominent role in the company, there may be more leeway in the use of resources in case there is a need to implement initiatives.
- **Leadership support:** Access in Takeda is strongly embedded in the core values of the company, not explicitly, but as part of the PTRB set of values. The president of Takeda has demonstrated on multiple occasions his commitment to working towards access. Parallel to that, the president of Takeda Vaccines, Rajeev Venkayya, who has a strong leadership background in public health endeavors[*] before entering pharma, has also shown strong belief in access as a core driver of Takeda Vaccines' business.
- **Individual interest:** A common denominator among multiple interviews was strong interest in the public health value of the vaccine company's work. Teams appeared genuinely interested in developing the right product to reach as many people as possible. They did not appear worried

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vaccines, and Takeda Vaccines in Japan only addresses the local market. In fact, these vaccines cannot become global; they are old products with high cost of goods (COGS) that would be unable to compete in the global market against the newly marketed vaccines.

[*] Previously Director of Vaccine Delivery at the Bill & Melinda Gates Foundation and Special Assistant for the President for Biodefense at the White House.

about the market and business aspects of the vaccine. Getting the vaccines to the people who need them appears to be the employees' true motivation. This opens the door to a value-driven environment with employees who are willing to accept changes in their way of working as long as the objective aligns with their beliefs.

- **Global ATM momentum:** After Takeda's successful result in the 2018 ATM Index report (Access to Medicine Foundation, 2018a), access is gaining extra traction within the organization. The company has released several internal notes as well as press releases that remark on the importance of Takeda being considered one of the leading ATM companies. This is an ideal opportunity for introducing new initiatives or structural changes. The supporting reason for these changes is that Takeda will need to do something different to retain its ranking in the next iteration of the Index[*].
- **Dengue:** The development of the dengue vaccine is reaching its last stages. In January 2019, the candidate reached the primary endpoint of its phase 3 trial. This means that the vaccine has very good chances of being launched in the near future. The availability of a product in the market is an excellent opportunity to introduce access initiatives.

The outcome of this analysis, expressed in five points, will help define a vision and approach to ATM that aligns with that of Takeda Vaccines while preserving Takeda's general vision and values. Data on trends in ATM obtained through conversations with external experts, and from the literature, also support the definition of the vision for Takeda Vaccines.

[*] Takeda's score is extremely close to a group of eight other companies behind it, and a small variation could push the company down in the ranking. In fact, Takeda in fifth position is as close to the second as it is to the thirteenth.

The following chart shows the **proposed Takeda Vaccines vision on ATM**:

Table 1. "The access manifesto". Takeda Vaccines access vision.

1	The **conceptualization of access** needs to be **revisited**. The company considers access not as a set of iniatives developed as part of a corporate social responsibility approach. Access is part of the company's identity.
2	The inherent public health nature of a vaccine does not mean that a vaccine company does access by default. A **proactive approach** to the development of access intiatives throughout the whole vaccine value chain is needed.
3	Access needs to be truly **integrated in the core business** of the company as an immediate extension of Takeda's values.
4	Access is only valid if the iniatives proposed are defined to some extent by **sustainability, measurability, and scalability**.
5	The gold standard for the company is to achieve the **access-by-default approach**. This implies that decision-making takes into consideration access implications as well as financial, business, etc. Furthermore, decisions that limit access should be justified.

Source: Author's own.

The development of the strategic vision is followed, as explained previously, by the definition of the strategic objectives that will lead to the identification of the right initiatives as the tool for achieving the strategic vision.

4.3 THE STRATEGIC OBJECTIVES

The definition of strategic objectives follows the SMART philosophy, meaning that they need to be:

- **S**pecific: They need to state the expected results clearly
- **M**easurable: They have to put forward concepts that can be evaluated
- **A**chievable. Objectives are of no value if they are unrealistic or outside the scope of what the company can achieve
- **R**elevant: They need to address the points addressed in the Access Vision
- **T**imely: A limited number of strategic objectives that are achievable within an acceptable timeline

Takeda does not have a standard means of defining strategic objectives. Therefore, the decision on how they are to be developed follows the author's strategic framework, as depicted previously in Figure 6. The objectives are developed taking into consideration the proposed strategic vision as a baseline. However, it is also essential to refer to the data from interviews and from analysis of the ATM Index. By doing so, it is possible to accurately define a set of critical, company-aligned, and attainable objectives.

The following table (Table 2) shows the four strategic objectives selected for Takeda Vaccines.

Table 2. ATM strategic objectives for Takeda Vaccines

Strategic Objective 1
Integrate ATM in the core business of Takeda Vaccines: Takeda's values and willingness to work on access should be accompanied by measurable initiatives. Decision-making processes should incorporate access as another variable to consider.
Strategic Objective 2
Push towards processes standardization: Standards are an important part of strategic coherence. Strategy development requires the standardization of procedures that will permit the replication of consistently successful initiatives.
Strategic Objective 3
Develop follow-up and accountability mechanisms: To address quality concerns, it is necessary to include mechanisms that will allow performance evaluations.

Table 3. ATM strategic objectives for Takeda Vaccines (Continued)

Strategic Objective 4
Integrate ATM as a sustainable activity: Takeda Vaccines' approach to access must consider the sustainability of its activities as a key factor.

Source: Author's own

Once the strategic objective has been defined, the next phase is the definition of the initiatives that will address these objectives.

5 PROPOSAL: INITIATIVES TO INDUCE A NEW APPROACH TO ACCESS TO MEDICINES IN TAKEDA VACCINES

The following initiatives have been developed taking into consideration the research results and Takeda Vaccines' proposed strategic vision on access to medicines (ATM).

The proposed initiatives address the four strategic objectives identified earlier. Each initiative is linked to one or two strategic objectives. They do not follow any particular order of importance or expected impact. However, they follow an ideal order of implementation based on the linkages among them and based on Takeda's working dynamics. Therefore, the first proposed initiative is easier to implement due to its importance and the lower cost (financial and strategic) of implementation. The second one will be the next initiative to implement, and so on.

These initiatives have been selected using the criteria of low cost and high expected impact. The organization does not have a working strategy on access nor a team dedicated full-time to the topic; hence, imposing significant structural or costly changes, whether organizational or financial, could exacerbate the normal reluctance of any organization to change. The idea is to develop initiatives that will not alter normal activities significantly to minimize concerns or backlash from teams or leadership.

The initiatives have been selected after careful evaluation of the strategic objectives together with the information obtained from the data gathering. Some initiatives arose during informal conversations, others through careful review of the ATM Index documents and best practices, yet others by observation of the internal dynamics and its gaps on access. Among them, only initiatives that align with the strategic

objectives were selected and adapted in a manner that would be attainable by Takeda Vaccines in the short- to mid-term[*].

The selected initiatives are depicted in the following table:

Table 4. Initiatives to induce a new approach to ATM in a vaccines company

1. Access Champion as part of the Global Product Team (GPT)
2. Key Performance Indicators (KPI) linked to access
3. Working Documents
4. Roadmap Development
5. Standardized Development of Initiatives

Source: Author's own.

5.1 INITIATIVE 1: ACCESS CHAMPION AS PART OF THE GLOBAL PRODUCT TEAM

The GPT is probably one of the most critical strategic governance structures throughout the vaccine value chain, if not the most critical. It is an intermediate-level decision-making body formed in the early stages of vaccine development, and follows the development until the product is released to the market, and continues monitoring it further.

The GPT does not have the capacity to make executive decisions; there are other hierarchical levels above it. However, it informs the decision-making as a group of experts on the product.

The GPT comprises one person from each team involved in the vaccine development, and who acts as its functional representative.

[*] The expectation is that in the next 2 years, all initiatives are in place and will yield consistent results between 3 and 5 years.

Justification of the initiative

The GPT goes through different stages on the long path of vaccine development. Despite the standardization of the GPT structure, roles will evolve. Depending on the stage of vaccine development, some GPT members may play a more relevant role than others. In general, this lead role corresponds to those whose job is related to the phase the vaccine is undergoing. For example, during the early development stages, the discovery representative of the GPT will have a more prominent role in decision-making than the GPT member from regulatory affairs or the market access teams.

Access is an aspect that carries more weight and consideration when teams linked to policy or market access take on this more prominent role in the GPT. However, access needs to have relevance throughout the whole vaccine development process.

Therefore, having a dedicated person as part of the GPT will ensure that access provisions will be considered throughout the whole vaccine value chain cycle.

Strategic objectives addressed

This initiative addresses the strategic objectives S1 (integration of ATM in the core business of Takeda) and S4 (integrate access as a sustainable activity).

Implementation

Although it requires low preparation and can be carried out immediately, the configuration of implementation can differ. The proposed alternatives are as follows:

- One person engaged full-time as an ATM representative
- An existing GPT member that takes on the responsibility for ATM (probably the GPT lead)
- Responsibility for ATM is a rotating role among the GPT members

Once the configuration has been selected, the next step is to choose two products (it would be unwise to start with all available products in the pipeline at the same time). As a product that is in the last stages of development and therefore more favorable to an access approach, the ideal candidate is the dengue vaccine.

The second candidate, selected from among those in the earlier stages of development, is the norovirus vaccine. This product appears to be ideal, as it fits the access paradigm: a vaccine aimed at children worldwide, but with a huge potential impact in low- and middle-income countries (LMIC).

Cost implications

The cost implications would vary with the type of implementation:

- If the person elected is already part of the GPT, the cost would be associated with the performing of one more activity. This is by no means a full job, but a parallel activity. It would require adapting the person's job profile.
- The other option of having an ATM person full-time in the GPT role would imply an extra Full Time Equivalent (FTE), which could be divided between the different GPTs.

Expected outcomes

The primary expected outcome of including one person who can push for access provisions in the early stages of the GPT is the possibility of developing products more aligned with the expected target population in the LMIC. Potential mistakes linked to the lack of definition in the early stages of the target population's characteristics can be reduced. Lobbying can be performed together with the policy or

market access teams for decisions that take into consideration the target population (i.e., when defining trial configuration[*]).

Another outcome is the development of synergies. Currently, the GPTs do not share a communication platform, nor are they expected to do so. The inclusion of an ATM-responsible member would mandate working together with the ATM champions from the other GPTs to share ideas, initiatives, and failures. This, in the mid- to long-term, will generate better understanding of the initiatives that would work better according to Takeda's culture and operational approach.

5.2 INITIATIVE 2: KEY PERFORMANCE INDICATORS

The use of key performance indicators (KPI) is standardized at Takeda, in part due to the financial incentive attached to them.

KPIs are structured in four categories:

- Divisional: The most relevant; divisional KPIs define the critical activities and objectives for the whole business unit. Divisional KPIs are validated by the corporate office and are measurable. Their outcome will define the bonuses employees will receive.
- GPT objectives: Second-level indicators. GPT objectives inform divisional KPI development. Takeda Vaccines is a GPT-centric organization, which means that the GPT has strong operational value; therefore, defining and achieving the GPT objectives are a critical part of the business.
- Functional objectives: These correspond to functional teams. Functional objectives are developed following the outlines defined by the GPT objectives.

[*] From an access perspective, an ideal trial would include a broad spectrum of population as well as multiple variables to consider (i.e. concomitancy). However, trials are lengthy and costly exercises, and compromises are required in order to gain registration as quickly as possible.

- Personal objectives: These are used to evaluate employee performance. Personal objectives are also linked to functional objectives.

Justification of the initiative

KPIs play an essential role in Takeda's operations. Objectives at different levels determine where individuals and teams should dedicate effort. Projects or activities not necessarily linked to KPIs risk losing importance in daily operations.

Unfortunately, no KPIs or objectives have been defined based on access. Therefore, asking teams or individuals to put time into developing access initiatives is unlikely to succeed. Therefore, adding KPIs related to access will make a dramatic difference in terms of involvement and accountability.

Strategic objectives addressed

This initiative addresses the strategic objective S3 (Develop follow-up and accountability mechanisms).

Implementation

Implementing KPIs related to access is a high-priority initiative that demands some savoir-faire. KPIs are intimately linked to jobs, so having buy-in from leadership is fundamental.

As stated earlier, divisional KPIs are the most critical KPIs. So, to avoid pushbacks and to ensure a smooth transition to this new access approach, the best option is to go through the second-level GPT objectives. However, the impact will not be limited to the GPT; it will trickle down to the functional and personal objectives and will have substantial significance not only at the second level but on the overall work of the Vaccine Business Unit (VBU).

It is important to also keep in mind that Takeda KPIs are developed and approved once a year, in April. Therefore, it is important not to miss this window of opportunity.

KPIs should be pushed to the division level once they have been implemented at GPT level and have shown buy-in by the teams. However, this will not happen immediately.

Cost implications

As the objective is to address GPT-level KPIs with no direct impact on financial incentives, there is no extra cost associated with fulfilling the initiative. There may be costs associated with KPI development and the actual implications of launching activities to address the KPI, but they cannot be evaluated at this stage.

The cost of establishing these KPIs would have a strong impact once (or if) they reach divisional level, as it could imply significant expenses for Takeda on employee bonuses. This cost can be forecast and included in budget provisions.

Expected outcomes

Incentives are the best means of motivation. In the short-term, KPIs will dynamize the access field in the organization, with teams being involved in developing and proposing access initiatives.

At the same time, KPIs also play an important role in normalizing activities. What starts as a KPI-linked initiative will, with time, become a part of the company routineembedded in the team's thought processes.

5.3 INITIATIVE 3: WORKING DOCUMENTS

Documents are a fundamental tool for vaccine development. They tend to follow a standardized structure, and are used to define a set of objectives, characteristics, considerations, and redlines that the team in charge should take into account.

An important characteristic of these documents and guidelines is that they are not set in stone; they allow a certain level of modifications along the vaccine value chain to adjust the product or expectations to new

realities or decisions. These modifications can take place due to a change in science, the epidemiology of the disease, the target population, and multiple other factors.

The documents identified as suitable for incorporation under the ATM strategy are the Asset Strategy, the Clinical Development Plan, and the Brand Development Plan. Another document, although quite often referred to independently, is part of the Medical Development Plan: the Target Product Profile (TPP). Due to its importance, the TPP is considered an independent part of the proposed initiative's package.

- **Asset Strategy**: The first document developed for a potential new product. It establishes the baseline for the future development of the vaccine. It contains a brief description of the epidemiology of the disease, a development strategy, and a set of scenarios (minimum case, base case, upside case) that defines the alternatives and options considered for the vaccine.
- **Clinical Development Plan**: The basic document that will be followed throughout the research and development (R&D) phase of the product. It includes the technical aspects of the vaccine, from disease epidemiology, the rationale for antigen and adjuvant selection, to clinical studies. However, it also includes more operational aspects such as publication plan, regulatory strategy, or goals for the vaccine. An essential part of the document is the roadmap to licensure, which includes the sequence of clinical trials, milestones, deadlines, and interconnected tasks. It also includes the TPP, discussed next.
- **TPP**: It is not a document per se, but a table. It defines a set of fundamental attributes (Efficacy, Safety, Administration, Patient/Economic outcomes, Other critical attributes) and defines objectives for each attribute and shows its completion status.
- **Brand Development Plan**: Similar to the Clinical Development Plan, but developed specifically for the late stages of the project. It depicts the strategies to follow for the product to enter the market and to maximize its impact.

Justification of the initiative

As Takeda has Patient as a core and fundamental value, the documents mention, in one way or another, the need to address patient needs. It could be inferred, therefore, that the plans and objectives included in the documents are defined through a patient-centered approach. Hence, the vaccines and linked initiatives will inherently be linked to access.

However, it may be argued that the only way to accept a valid approach to access is to include in the documents specific points that explicitly establish access objectives, priorities, and deadlines. So far, the documents contain no mention of access provisions.

Strategic objectives addressed

This initiative addresses the strategic objectives S1 (integration of ATM in the core business of Takeda) and S4 (integrate access as a sustainable activity).

Implementation

The implementation must follow a structured approach. Here, the GPT leader and GPT coordinator should validate it. As each document is different, the incorporation of access provisions will vary between them. The general shared idea is that each document will contain a relevant point on access that will include at least a rationale and objectives.

The TPP is a particular case, being a chart that depicts a set of attributes. However, as it is a reference tool for the GPT, its potential impact on product development is considerable. Two proposed implementation options are related to the TPP (see Appendix 9.8):

- Access as another attribute: It will have a moderate impact
- Access as a characteristic that must be addressed by the different and already defined attributes. This is a high-impact option

Cost implications

This initiative will imply negligible extra costs, as the documents and people involved are part of the routine work. The only cost is the time involved in the decision and the development of the final layout of the documents.

Expected outcomes

Including access provisions in the official documentation is a critical step forward in acknowledging access as a core part of the organization. So far, and besides Takeda's values and its patient-centered approach, it is not possible to track access initiatives through documents or to justify decisions made for or against an access approach. Introducing explicit points on access into documents will push the GPT into discussions on the possibility of implementing access initiatives, approaching the "access by default" approach shared in the proposed vision.

5.4 INITIATIVE 4: ROADMAP

A roadmap is a tool that demonstrates a program's different milestones, processes, or deadlines. It is a standard tool; in fact, Takeda Vaccines already uses one to follow-up activities in its Clinical Development Plan. What is not common practice is developing a roadmap for access initiatives or including access initiative milestones into the existing operational roadmap.

Justification of the initiative

As mentioned above, Takeda is already using a roadmap in its Clinical Development Plan. However, the roadmap is limited to the clinical operations related to vaccine development, from pre-clinical to licensure; there is no mention of potential access initiatives.

Currently, GPT's project manager does not have a clear understanding or a full overall perspective of the potential access activities and decisions. They need to be aware of what these activities are, and when they can be implemented along the different phases of vaccine development. With the roadmap, access opportunities will be more patent not only to the project manager, but to all GPT members. The teams will be able to visualize and understand access as a continuum, and not only as a late-stage activity.

Strategic objectives addressed

This initiative addresses the strategic objective S3 (Develop follow-up and accountability mechanisms).

Implementation

This initiative requires GPT leadership authorization as well as coordination to determine the ideal type of implementation. There are two options, with the accompanying pros and cons:

- An independent roadmap to be included with the Clinical Development Plan. This is a "cleaner" option. However, it may feel isolated and not necessarily linked to existing processes and milestones in the different teams.
- Integration with the existing roadmap to licensure. This option is more coherent and useful because it will allow connection and visual contextualization with existing activities. However, it can also become too confusing, given the existing number of processes in place.

Another critical part of the implementation is developing a list of potential initiatives and best practices, adopted from the industry, as a baseline. This will be used as a solid foundation for activities that can be incorporated during the implementation of the roadmap. With time, Takeda teams will be able to develop their own set of initiatives or to adjust the proposed list in a manner that better aligns with the specific product and Takeda's understanding of access.

Estimated cost

Similar to the working documents initiative, this initiative will only imply costs in the conception and development of the roadmap. It does not imply any extra costs or resources, as the documents and people involved are already part of the routine work.

Expected outcomes

GPT leadership and member awareness of milestones related to access.

Enhanced visibility of access throughout the vaccine value chain. This will help build the idea that access is part of the whole R&D process and not only a commercial activity. GPT members will be aware from the beginning of the impact of access at different stages.

Identifying milestones and windows of opportunity for access activities will enable, for example, forecasting the development of studies, or ensuring that the information is available to make the right decision when at the required time. This will avoid missing redlines that could have substantial implications on access[*].

5.5 INITIATIVE 5: STANDARDIZED DEVELOPMENT OF INITIATIVES

Currently, Takeda Vaccines does not have an overall access strategy. Therefore, initiatives do not follow a predefined conceptual framework for development, nor a shared structure or log frame. This precludes the comparison and measurement of different activities. In addition, the absence of guidelines, including the obligation to establish indicators for each initiative on access, will prevent the development of

[*] Missing redlines on access is one of the main concerns about which ATM teams should worry. As an example, once the decision on manufacturing a mono-dose vial vaccine has been made, there is no easy way back. If for any reason the decision changes to a multi-dose vial to expand access, the new product will take extra years to be available.

evaluation standards. The absence of these standards will lead to missed opportunities for measuring the impact and success of the activities.

Justification of the initiative

Processes standardization helps establish baselines that will enable comparison and understanding of the improvement brought by initiatives. This is even more necessary when dealing with a quality improvement framework. In this case, standardization is not only useful but is also essential.

Strategic objectives addressed

This initiative addresses the strategic objectives S2 (push towards processes standardization) and S4 (integrate access as a sustainable activity).

Implementation

The success of the implementation of this initiative is linked to two main factors: the ideation of an adequate development framework, and the adoption of this framework by the teams. These factors have their complexities:

- Team adoption: As with any change in work procedures, teams will have to undergo training. However, another factor cannot be overlooked: the willingness to accept change. Employees must understand the value of the change for it to crystallize.
- Initiatives development framework: The complexity of this issue lies in finding the right approach that will encompass a myriad of initiatives not necessarily related to each other. A potentially useful

framework could be similar to the logic model used by Boston University in their Access Observatory 2018 Report* (Laing et al., 2018) to evaluate the program impact of pharma projects linked to access.

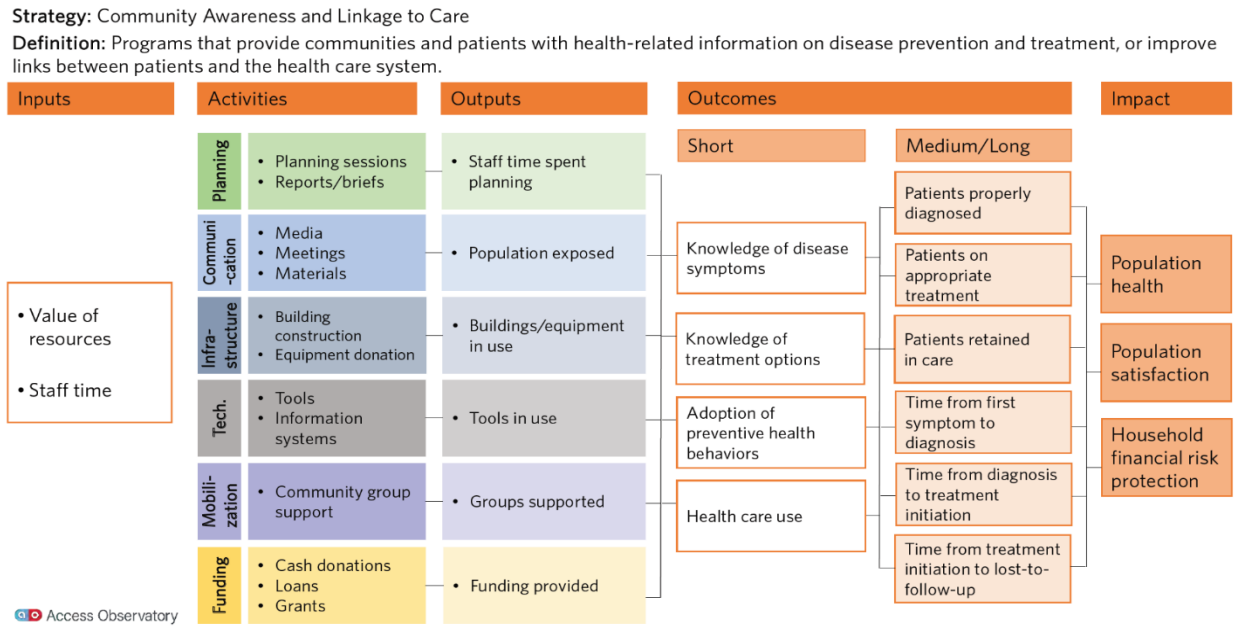

Figure 8. Example of log frame for access initiative development. Source: Laing et al., 2018

Cost implications

The main cost linked to the development of this framework is the time used for its conception. However, financial implications can be substantial once initiatives are launched, as this approach will imply investments in the evaluations of the initiatives.

* The Boston University Access Observatory is a "public reporting platform for programs that aim to improve access to disease prevention and treatment services in low- and middle-income countries." Although this platform and mechanisms have been designed for the Access Accelerated initiative (focused on private sector engagement on NCD [noncommunicable diseases] prevention and treatment), it has also been designed to potentially address any other kind of access program.

Expected outcomes

As mentioned earlier, the value of this implementation is:

- A more comprehensive approach to access through standardization of the conceptualization and development of activities.
- Better access outcomes in the mid-term due to the possibility of evaluating, measuring, and learning from other, relatively less successful initiatives.
- Enabling the potential replication of initiatives based on process standardization. This will lead to easier initiative development and better adoption of access dynamics and mindset.
- Standardization will enable better analysis of the activities launched and better understanding of potential gaps.

6 NEXT STEPS: A FRAMEWORK TO LEAD STRATEGY INTEGRATION

Defining the strategy is essential, but so is knowing how to integrate it seamlessly into the organization. Failing to implement an access strategy appropriately could lead to disengagement from access as a concept and discourage future efforts.

To define how a new strategy on access is adopted, it is necessary to dive into the organizational business literature, even if the examples are not limited to or are wholly unrelated to pharma.

One of the best available options is the work by Yuan et al.(2011) on strategy integration.

6.1 STRATEGY INTEGRATION FRAMEWORK

This framework can help address how an ATM strategy can be integrated into the core business of a pharmaceutical company. This specific concept has not been studied before; however, the literature on corporate social responsibility (CSR) strategy integration in the core business of a company can be used, to some extent, as a good proxy. CSR, as well as access to medicines (ATM), involves an innovative approach to initiatives that may not be, at first sight, beneficial from the business perspective. Both also attempt, to some extent, to change the culture of a company by incorporating a more

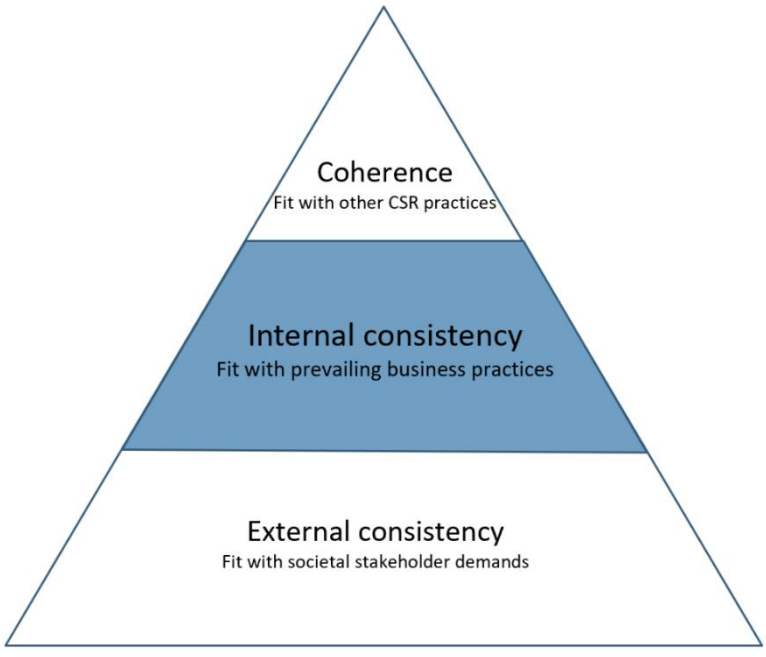

Figure 9. Fit of CSR activities into an existing organization. Source: Yuan et al., 2011.

ethical approach in the organization. In both cases, incorporating new activities may cause interference and will have to link with existing processes, which can be challenging.

So, taking this as a reference, the framework developed by Yuan et al. in "Integrating CSR Initiatives in Business: An Organizing Framework" (Yuan et al., 2011) appears to be a perfect fit. The authors focus on the aspect of internal consistency when introducing new activities, and how linkages between them can be created to avoid disrupting the organization's core activities (Figure 10). The present work studies how this integration takes place, the peculiarities of the system, as well as considerations to keep in mind to increase the options for an internal fit.

The proposed framework addresses the idea of internal consistency and the concepts of core and periphery activity* by defining seven patterns for integration. In this specific case, integration requires creating new activities and routines, termed patching.

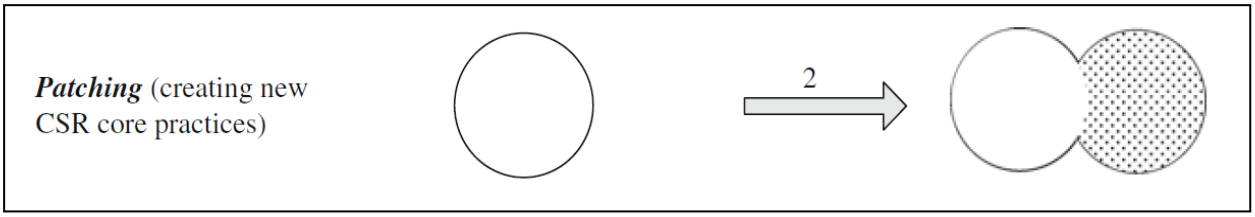

Figure 10. Patching strategy for initiative adoption through core–periphery lens. Source: Yuan et al., 2011.

The first requirement of "patching" is the need for leadership to build and institutionalize values that will drive these activities. Fortunately, Takeda has already done so through their Patient-Trust-Reputation-Business (PTRB) approach.

* According to Yuan et al. (2011), core elements are internal elements that define the organization, objectives, and core technologies. Peripheral elements are the operational decisions and "arrangements undertaken either to align the organization with its environment or to buffer its core from external fluctuations."

The second key factor that defines this type of integration is the development of incremental organizational learning. By small incremental changes, this approach will, in the mid-term, lead to the objective of making ATM "an integral part of everyday business decisions, not only at the managerial level but also at the operational level, mainly through routinised […] planning and control processes with key performance indicators (KPIs)."

According to the authors, patching tends to be slow and requires "clear performance measures" and "related incentives."

The work of Yuan et al. has not only helped define the steps to follow, but also strengthened the present project's approach, as they point out initiatives that align to ideas that have been considered through strategy development:

- Corporate values
- Leadership support
- Step-by-step incremental change
- Adequate incentives
- Establishment of measurement and evaluations tools

7 CONCLUSION

Vaccine and pharmaceutical companies are undergoing a transitional moment regarding access to medicines (ATM). The time when donations were an acceptable strategy is long gone, and society demands more. The world's wealth is increasing, and countries are transitioning from access programs without clear perspectives on how they will cope with newly acquired health costs (Saxenian et al., 2015). Despite global interest, countries and organizations lack real commitment to aid the development of vaccines through coordination or financing, with CEPI (Coalition for Epidemic Preparedness Innovations) being one of the very few recent initiatives successfully launched[*]. Moreover, public perception of pharmaceutical companies is at a historic low[**] (Gallup, 2018).

This environment presents a series of opportunities for a vaccine company willing to go the extra mile and put forward an innovative approach to ATM. This may be an excellent opportunity for the private sector to step in and genuinely engage with the public sector, not on a transactional basis, but with a different model.

This project aims to establish the grounds for that. However, before innovative access strategies can be proposed, the company must integrate an access approach into its core business. Only by enabling a cultural change will the company generate a bold and sustainable approach to access.

Cultural change is not easy; it takes effort, time, and resources. Above all, it requires a genuine underlying interest, not only from leadership but also from the employees. Takeda Vaccines has created an ideal environment for this to take place. Its vaccines pipeline (dengue, Zika, norovirus, polio) is a bold

[*] It has been "successfully launched" but it is still too early to prove its validity as a successful model.
[**] Historic data from 2001–2018 Gallup surveys about public perception of US business. The pharmaceutical industry is considered "somewhat negatively" or "very negatively" by 53% of the respondents, the lowest point in the period considered.

declaration of its intentions. The company's efforts are focused on diseases with a strong and disproportionate impact on the low- and middle-income countries (LMIC). This approach has already set the bar.

This research proposes a framework and set of initiatives that will encourage and enable the development of more accessible vaccines. This project is adapted to Takeda's vision, goals, and way of working. The proposed initiatives are low-cost and technically easy to implement; they do not require substantial structural changes and will not affect the normal workflow of the company dramatically. However, they have the potential to change the way vaccines are developed. They could bring the concept of access down from the conceptual and ideological realm to the implementation sphere. This approach will guarantee that access has a place at the table where decisions are made. Together with the cost of goods and return on investment, it will now be another variable in the equation.

Change is never easy, so it would be naïve to expect that things will change drastically from one day to the other, where companies prioritize access over other business decisions. However, that is not the aim of this strategy. We are far from a future where access is the main factor in decision-making. The industry needs to start rethinking its approach to access and view it as a holistic endeavor throughout the whole lifespan of the product. Only when companies understand that access plays a role in every step of the development of a vaccine or drug will things start to change.

This is what this project is aiming for: to engage a vaccine company on a journey through incremental changes in critical areas that will yield strong results towards the adoption of access as a core value and, eventually, as a business driver.

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9 APPENDICES

9.1 DIFFERENCE IN MARKET AND ACCESS BEHAVIOR BETWEEN VACCINES AND PHARMA

Although it is generally accepted by the industry that the vaccines and the medicine (non-vaccine) markets are different due to the characteristics of their products, it is difficult to find robust studies or literature on the comparison between them.

However, it is possible to showcase these differences by selecting different parameters and analyzing how pharmaceutical companies behave depending on the product they sell. The option selected to identify what parameters can be evaluated is through the Access to Vaccines Framework (see Appendix 9.3). This framework, developed by the Access to Medicines Foundation in 2015 was used to evaluate the impact of vaccine companies on ATM on a report released in 2017.

The aim is to use this framework to showcase not only potential barriers to vaccine access but also to compare both business models in relation to access.

Only some of the sub-categories of the framework are displayed; some do not differ drastically between medicines and vaccines and some are not applicable in a way that is meaningful to the exercise.

This is not a comprehensive list of initiatives on access but a set of selected examples[*]

[*] Information obtained through interviews with Takeda employees and literature review. Although it can be argued that some drugs don't behave as stated, this exercise aims to show the general trend that characterizes the business model.

RESEARCH AND DEVELOPMENT

INVESTMENTS

- **Vaccine markets**: There is a limited number of producers and products in the market since it is a challenging environment for investments (Plotkin et al., 2017). Access implications: Sales can be forecasted since it is possible to know the expected demand through national immunization programs (NIP), companies can adjust prices and aim for high volume.
- **Medicine market (no vaccine)**: A higher number of products and producers. Access implications: Market dictates prices. Generics may play an important role (Haas et al., 2005).

AFFORDABILITY

PRICING STRATEGY

- **Vaccine markets**: Price does not have a direct impact on the general population since most of the vaccines are delivered through the NIP (Reid and Fleck, 2014). Access implications: Poses a significant financial burden in governments.
- **Medicine market (no vaccine)**: Although some countries provide the drugs through their health programs, out of pocket expenditure plays a significant role (Kamal et al., 2019). Access implications: Problems of affordability to a fraction of the population. Some access interventions could aim to target specific population groups.

REGISTRATION

- **Vaccine markets**: Complex regulatory pathways in LMIC (Milstien and Belgharbi, 2004) . Access implications: the consequences of licensing mismanagement and delays have a substantial impact on access. Working towards process standardization and planning may guarantee better access outcomes

- **Medicine market (no vaccine)**: Licensing protocols vary between products and countries. Is not possible to define a general SOP that fits every kind of drugs due to this lack of standardization.

LOCAL BARRIERS

- **Vaccine markets**: Extreme complexity due to cold chain and stockpile requirements (mainly for LMIC) (Ashok et al., 2017). Access implications: Adequate product profile in terms of dosage, thermostability, packaging requirements to country's standards will allow better and cheaper management
- **Medicine market (no vaccine)**: Products with different characteristics. It is not possible to have a unique procurement strategy. Access implications: Pharma can benefit from supply chain agreements with procurement companies for specific products

MANUFACTURING AND SUPPLY

ALIGN SUPPLY AND DEMAND

- **Vaccine markets**: Supply needs will depend on the adoption of the vaccine by the NIP programs[*]. Access implications: Once a vaccine is accepted as part of the NIP, supply availability for the target population needs to be ensured.
- **Medicine market (no vaccine)**: Most of the countries have a national essential medicine list (EML) (WHO, 2017). However, this is a list of minimum requirements. Only part of the drug industry is affected by it. Access implications: Those drugs not considered as part of the EML may not be available or subsidized by the country's price schemes.

[*] Countries are free to choose the composition of their NIP. WHO to help on that decision, has defined a set of guiding principles and considerations (WHO, 2012b).

- **Vaccine markets**: Purchased by governments or facilitated through mechanisms and organizations like GAVI, UNICEF or PAHO. Access implications: These entities aim to lower prices of vaccines for those countries that cannot afford "standard" market prices.
- **Medicine market (no vaccine)**: Supply is primarily managed by the private sector (once government authorizes the product). Entities like The Global Fund* (GFATM) have a role to play but as in this example only for a few diseases and drugs in a few qualified countries, what is not representative of the whole pharma environment. Access implications: Tiered priced strategies** have been widely implemented in the past, however its validity as a robust approach to improve access has been challenged (Moon et al., 2011).

VACCINE SECURITY

- **Vaccine markets**: Vaccines are closely linked to public health programs. This implies that companies need to ensure enough quantity and quality of the product to supply to countries to cover their target population***. Access implications: Need for R&D investment in streamlining production processes and cost reduction to guarantee enough vaccine supply by companies (cost effective).
- **Medicine market (no vaccine)**: Not such thing as security-related implications since the availability of suppliers for the most common drugs included in the EML is in general guaranteed.

Other aspects that are not captured but the selected framework but that define the core values of vaccine products are:

* The GFATM is an organization aimed tackle the impact of AIDS, tuberculosis and malaria.
** Strategy to drive down drug prices in LMIC subsidized partially by higher prices charged in industrialized countries.
*** Shortage scenarios are not uncommon even in advanced economies. Only in the period 2000-2006, the US experienced vaccine shortages on 9 different diseases (Hinman et al., 2006).

INTELECTUAL PROPERTY RIGHTS

- **Vaccine markets**: Property rights will expire after a certain time. Access implications: High entry barriers in vaccines do not allow new actors to take advantage of the property rights expiration (Plotkin et al., 2017).
- **Medicine market (no vaccine):** Property rights will expire after a certain time. Access implications: Prices will reduce due to the entry of new producers.

RISK

- **Vaccine markets**: Vaccines are administered to healthy patients. Access implications: Efforts on communication from the government side are required (Sadique et al., 2013)
- **Medicine market (no vaccine)**: Patients are willing to accept higher risks.

TARGET MARKET

- **Vaccine markets**: High population volume. Access implications: vaccine companies can work on lower prices due to a high guaranteed volume (GAVI, 2012)
- **Medicine market (no vaccine)**: Cannot guarantee a sales volume. Access implications: pharma may want to give price reductions/donations for certain drugs regardless of the volume if they can compensate with other markets (tiered pricing).

9.2 TAKEDA GLOBAL ATM. INITIATIVES DIAGRAM OVERVIEW

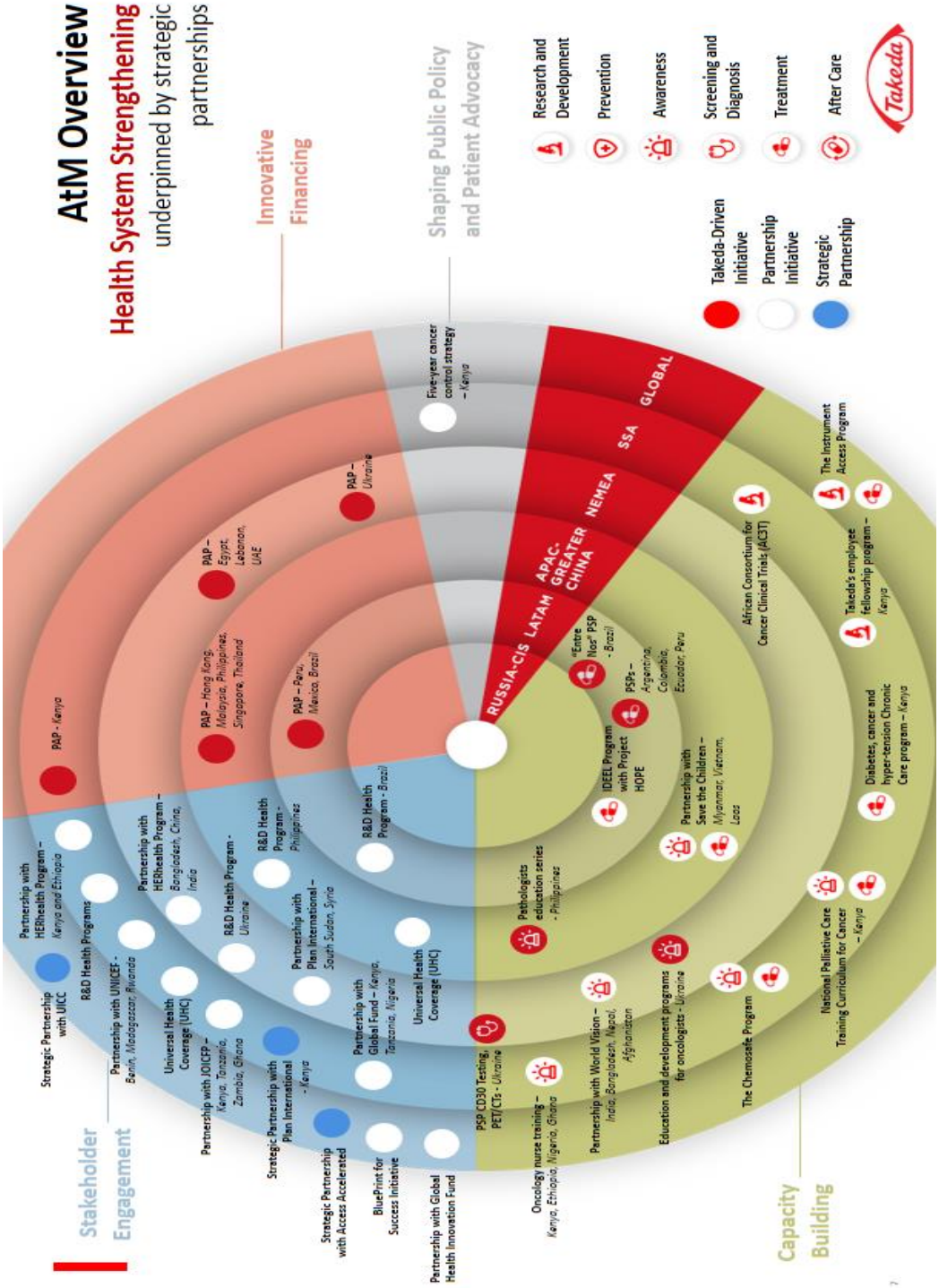


Figure 11. Takeda ATM global activities. Source: Takeda ATM Global Office

9.3 ACCESS TO MEDICINE FOUNDATION (ATMF): FRAMEWORKS

The ATMF is a nonprofit organization created in 2004 in Holland aiming to rank pharmaceutical companies on their efforts to improve Access to Medicines. The foundation is supported by the UK and Dutch governments as well as by the Gates Foundation.

The ATMF has developed two frameworks, adapted to the vaccine and pharma business, that help to identify barriers and opportunities for access. The frameworks correspond to the 2017 Access to Vaccines Index and the 2018 Access to Medicines Index.

The following frameworks are slightly different, not only due to their focus, either on vaccines or the whole pharma business, but also in their scope. The vaccine framework seems more restrictive. Something to consider is that the pharma framework is more refined, having gone through six iterations with the subsequent evolution and fine-tuning, allowing to adapt to new trends on access. So, even though it may seem that the vaccines framework could be more relevant for a vaccine company, for this project, the decision has been to rely on the general pharma framework (ATM Index).

ACCESS TO VACCINES FRAMEWORK

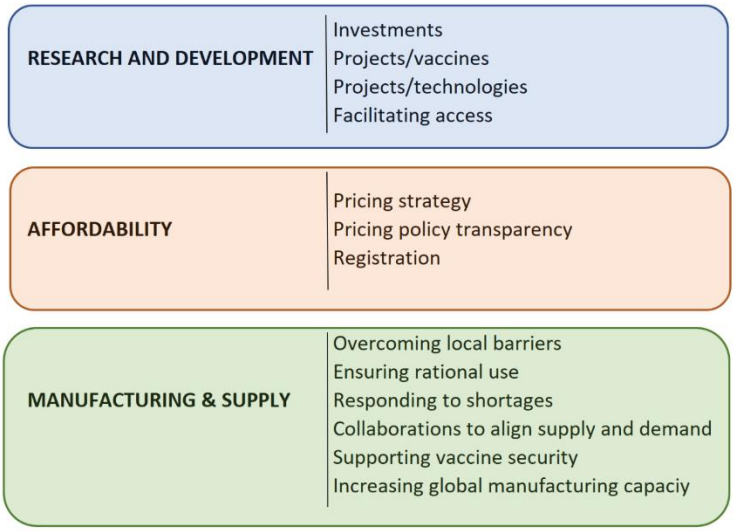
The development of the framework is based, on the one hand, on the Global Vaccine Action Plan (GVAP)* and on the other hand, on the experience dealing with stakeholders during ten years of the Foundation's work and translated it into vaccines.

The Foundation´s analysis has led to the conclusion that even though there is a multiplicity of factors that can be controlled by a pharmaceutical company that have implications for access, in the vaccine business,

* Framework approved by the WHO in 2012 aimed to deliver universal access to immunization. This initiative is supported by WHO, the GAVI Alliance, the Bill & Melinda Gates Foundation, the US National Institute of Allergies and Infectious Diseases, UNICEF, and the African Leaders Malaria Alliance (WHO, 2013)

"access to vaccines rests primarily" on three areas: Research & Development, Affordability, Manufacturing & Supply (Access to Medicine Foundation, 2015).

Table 5. ATV Index list of indicators.



Source: ATMF

ACCESS TO MEDICINES INDEX FRAMEWORK

This framework, developed in 2017 for the 2018 ATM Index analysis, is a more comprehensive version than the vaccines one. They have considered the idea of incorporating access provisions in earlier stages of the drug development cycle. This is a more robust framework that brings a broader approach to Access, including factors not considered as critical in the vaccine framework like Intellectual Property, capacity building, compliance, and general management.

This framework (Table 6) is more aligned to the holistic approach that this thesis is trying to develop. So even though the vaccine framework is still useful to identify some specific key vaccine capacities to explore, the Access to Medicines Index framework is presented as a better tool to explore potential improvements in the development of a strategy for a vaccines business.

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Table 6. ATM Index list of indicators.

MANAGEMENT	ATM Strategy Manage for ATM outcomes Stakeholder engagement Innovation
MARKET INFLUENCE & COMPLIANCE	Ethical marketing and anti corruption Responsible lobbying Compliance Innovation
RESEARCH AND DEVELOPMENT	Product development Planning for access Clinical trial conduct Innovation
PRICING, MANUFACTURING & DISTRIBUTION	Filling for marketing approval/reg. Equitable pricing strategies Manufacturing & distribution Innovation
PATENTS & LICENSING	Patenting strategy Licensing Competition Trade policy Innovation
CAPACITY BUILDING	R&D Capacity building Manufacturing capacity building Supply chain capacity building Pharmacovigilance capacity building Health system strengthening Innovation
PRODUCT DONATIONS	Scale & Reach Quality and sustainability Ad hoc donations

Source: ATMF

9.4 KEY ATM VBU INITIATIVES

The following list presents the set of initiatives on access that Takeda Vaccines has been involved in the period 2016-2017. A version of this list is part of Takeda Pharma's submission to the Access to Medicines Foundation for the 2018 ATM Index report.

Takeda vaccines is involved in the following initiatives:

- Expediting Access to Vaccines: Recognizing that communicable and neglected tropical diseases disproportionately affect countries with evolving healthcare systems, Takeda is collaborating with partners to expedite access to its potentially life-saving vaccine candidates, which address some of today's most challenging infectious diseases such as dengue, Zika, norovirus, and polio.
- Phase 3 clinical trials for Takeda's dengue vaccine candidate (TAK-003) began in 2016. In April 2017, Takeda announced completed enrollment of more than 20,000 children and adolescents in the global Phase 3 trial of its dengue vaccine candidate
- Takeda is investing more than 100 Million Euros in building a new manufacturing plant in Singen, Germany for its dengue vaccine candidate to ensure that we have sufficient supply of vaccine to meet global demand
- The US government through BARDA (Biomedical Advanced Research and Development Authority) has selected Takeda's Vaccine Business Unit to develop a vaccine to support the Zika response in the US and affected regions around the world. In early 2018, FDA granted Fast Track designation for our Zika vaccine candidate
- Takeda is partnering with the Bill & Melinda Gates Foundation to develop, license and supply at least 50 million doses of a polio virus vaccine annually for a period of ten years at affordable prices to more than 70 countries

- Takeda serves as a founding member of the Global Health Innovative Technology (GHIT) Fund, a pioneering, non-profit public-private partnership to promote the discovery and development of new drugs to fight communicable diseases. Takeda is a collaborative partner through GHIT on projects for malaria, tuberculosis, Chagas disease, and Leishmaniasis. In June 2017, Takeda committed US$5 million to support the GHIT Fund for the next 5 years (FY2018 to FY2022).

OTHER INITIATIVES ORGANIZED BY CATEGORY[1]

MANAGEMENT

Governance

- Takeda has formed Vaccine Regional Leadership Teams in the Asia Pacific (APAC) and Latin America (LATAM), ensuring continuing engagement for Dengue vaccine on both regional and local levels (covering at least the seven key dengue countries and PAHO supply by Q4 2017)

RESEARCH AND DEVELOPMENT

Post-trial access – regulatory filings

- Takeda's Vaccines Business Unit (VBU) has publicly committed to submitting local registration filings to ensure post-trial access to vaccines in all countries where clinical trials have been undertaken, including those within the scope of the index.

Innovation in Vaccines

- Takeda VBU Research to understand the evolution of immune responses to dengue vaccination in dengue-endemic areas

[1] Following the structure of the ATM Index Framework 2018

- Research on the interaction among dengue and Zika in pathogenesis and immunity, in collaboration with Dr. David O'Connor, University of Wisconsin.
- Takeda VBU is taking an innovative approach of reviewing alternative licensure tracks to ensure our candidate Zika vaccine is made available to populations in the shortest amount of time and in circumstances where there is potentially insufficient local transmission, during the clinical trial period, due to reduced epidemic severity. Success would allow us and others to have a pathway to license the vaccine ready for when Zika re-emerges.

PRICING, MANUFACTURING, AND DISTRIBUTION

Innovation in pricing manufacturing and distribution

- In addition to the manufacturing and distribution agreements mentioned above, Takeda is also exploring innovative financing models to support Middle-Income Countries related to the affordability of large dengue immunization programs. Takeda is on an exploratory phase for these models but plan to engage with key external stakeholders to develop access programs which meet large, underserved populations.

PATENT AND LICENSING

IP sharing

- Takeda is a member of WIPO, a global initiative which uses public-private partnerships to promote and facilitate the sharing of IP assets to accelerate the development of technologies for malaria, tuberculosis (TB) and neglected tropical diseases (NTD's).

The implications have been:

- In June 2016, the Global Alliance for TB Drug Development and Takeda announced that they have entered into an agreement that further explores hits generated from a high-throughput screening

program conducted to find novel compounds to improve treatment of tuberculosis (TB). The joint research program is funded through the GHIT Fund. The TB Alliance is permitted to find hit compounds with Takeda's virtual screening technology and compound library.

- In November 2017, Takeda and NIH entered into a joint venture to examine the feasibility of using Takeda's microneedle patch technology to administer a protein antigen-based, transmission-blocking malaria vaccine developed by NIH's Laboratory of Malaria Immunology and Vaccinology.

Anti-competitive behavior: trade policy

- Takeda's approach to Intellectual Property (IP) aims to create a balance between accelerating the expansion of patient access to medicines while fostering the long-term development of new, potentially life-saving medicines and vaccines.
- Takeda's position on patenting and licensing provides opportunities for qualified generic firms to manufacture and deliver our innovative medicines and vaccines. Takeda's IP policy is innovative in its ability to support the development of potentially life-saving drugs while promoting access for those countries which lack the necessary resources. Takeda's policy covers patents for both medicines and vaccines, the latter of which are vital in many of the environments which characterize LDCs.

Innovation in patents & Licensing

Takeda has taken an innovative approach in the way it has approached patents in LDCs. We believe that IP should not be a barrier to access and have committed to the following in LDCs and LICs, which include AtM Index countries:

- Either not to file a patent or not enforce it
- To support voluntary licenses and non-assertion declarations or clauses where necessary to improve access to medicine

- To offer, under appropriate terms and on a selective basis, licenses to manufacturers that can provide low-cost access to our medicines
- To make our patent information available on request to the public.

CAPACITY BUILDING

Research and Development

- A dry run clinical trial was implemented as part of the Takeda Dengue Vaccine Candidate Phase III pivotal Efficacy Trial in eight countries. This strategy is considered to serve as a major capacity building initiative, strengthening the current and future capability of the site to deliver this and other complex trials.
- Takeda Global Investigator Initiated Sponsored Research Program (IISR): Building local research capability and providing access to innovative medicines with a special focus on Dengue as a cause of non-malarial febrile illness in Southwestern Uganda.

Manufacturing

- Collaboration with Zydus Cadila to develop a vaccine against Chikungunya. The goal of the collaboration is to develop the vaccine candidate through preclinical testing, phase 1 and phase 2 clinical trials in India through the efforts of Zydus Cadila with support from Takeda. Takeda will continue the Phase 3 clinical development. The collaboration also includes process, assays and formulation development, production of clinical materials and commercial supply of the vaccine.
- Collaboration between Takeda and Biological Limited to develop low-cost measles-rubella (MR) combination vaccine for low and middle-income countries. The goals of this initiative are: Technology transfer of the Takeda measles vaccine process to Biological E, Process development to improve yields and reduce cost of goods at Biological E, conduct clinical trials of the combined measles-rubella vaccine in India and other countries, pending successful trials produce commercial supply of the MR

vaccine in India at the Biological E site, if useful, transfer the new manufacturing process developed by Biological E to Takeda's site in Japan.

Pharmacovigilance

- Takeda is actively engaged in the World Health Organization's (WHO) Global Vaccine Safety Initiative, an important initiative aiming to deliver vaccines support to resource-limited countries. The objective of the initiative and Takeda's involvement is to promote improvements in pharmacovigilance processes in resource-poor countries through the provision of technical support and training.

Health system strengthening

- Takeda participates in and contributes to pharmaceutical research supporting the development of innovative, outstanding products for patients of Neglected Tropical Diseases NTDs by using advanced technologies for drug discovery research and proprietary compound libraries.
- Takeda aims to develop new treatments for NTDs and other poorly served conditions. To do so, it has prioritized partnerships and collaboration with external organizations like the Global Health Innovative Technology (GHIT), on innovation for infectious diseases of the developing world and the Bill and Melinda Gates Foundation, to develop and supply the sIPV vaccine to more than 70 developing countries.

Innovative research approach

- Takeda is currently leading various innovative research approaches to the development of critical products in a way that will promote greater access to medicines in both developing and developed countries alike. Takeda's innovative research has the potential to bring about a transformation in the kind of and the way in which medicines are delivered to individuals, particularly within Index Countries.

Takeda's Micro-Needle Patch Technology for Malaria DNA Vaccine Development is one of the innovative research projects currently underway.

9.5 INTERVIEW QUESTIONS

The interview process aims to gather information regarding internal processes, access related activities, hierarchical structure, communications, and in general, different aspects of the operational job

- What department do you belong to?
- What is your position in the hierarchical structure?
- What are your main job's tasks?
- Do your assigned tasks require you to interact with other departments? If yes which one? How often?
- What are the main tools that your department uses to define objectives?
- While in your current position, have you received any training or communication related to access or access to medicines?
- Can you name any access activities performed by you or your department?
- Can you name any access activities performed by any department at the VBU?
- Can you name any access activities performed by any department at Takeda?
- Have you ever engaged in discussions regarding the development of access initiatives in your department?
- Is there any potential access initiative that you can think of that your department could be doing?
- Can you think of any opportunity in the mid to long term for your department to engage on access?
- Do you see any value/burden that developing access initiatives could mean to your job?
- Are you aware of Takeda's PTRB values? Do they translate into the decision making process in your department? If so, how?

9.6 ATM INDEX ANALYSIS: QUANTITATIVE VISUALIZATION

The data to generate the following chart has been obtained through the analysis of the different weight of the indicators. The color code corresponds to the interpretation of Takeda's submission together with the comments by the ATM Index reports.

This is an approximate visual interpretation of what the ATM index means. There may be other qualitative parameters (not considered in this quantitative evaluation) that the FATMF may also use as variables that influence the final ranking.

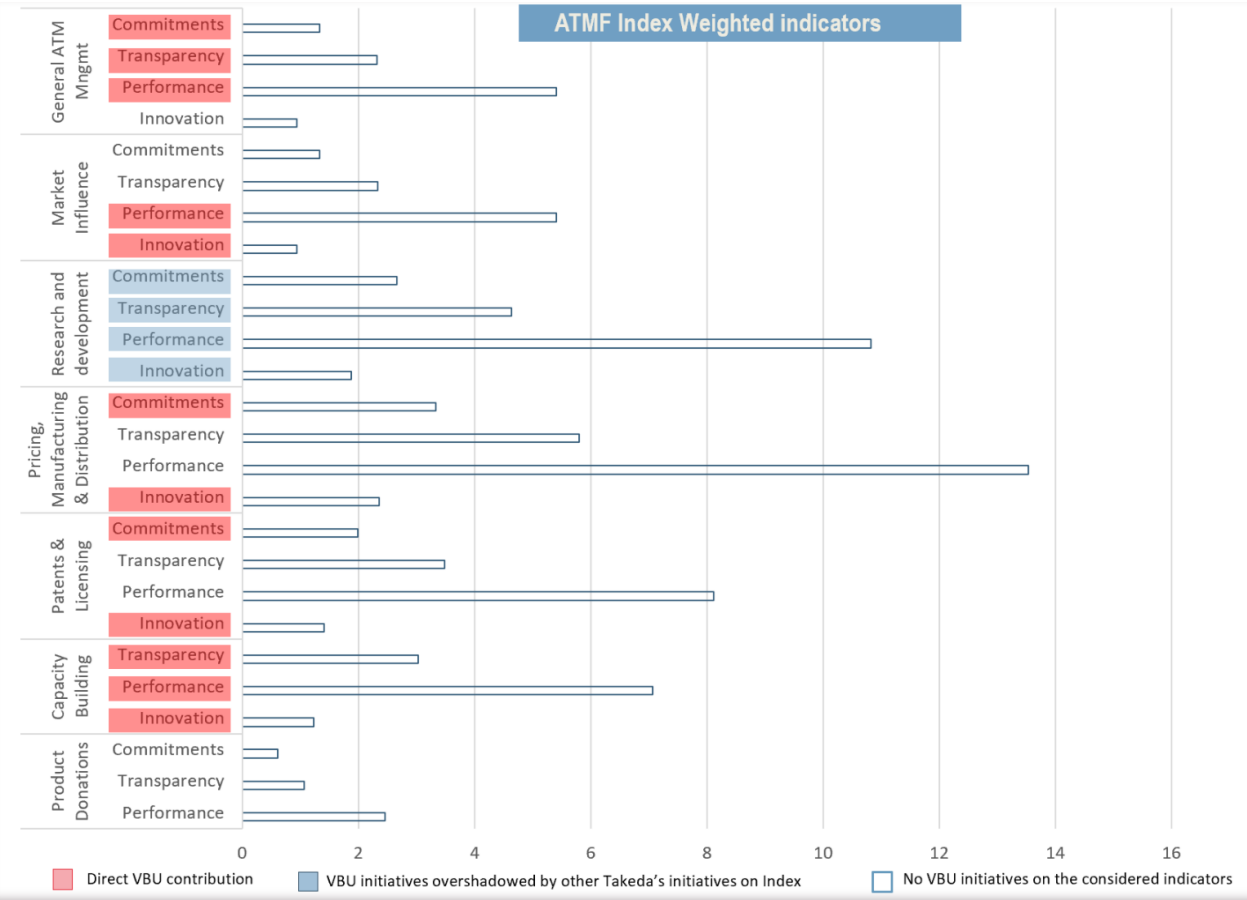

Figure 12. ATM Index analysis interpretation for Takeda Vaccines. Source: Author's own

- This chart is an interpretation of the quantitative and qualitative data scattered through three different documents: The ATM Index Report 2018. The ATM Index Methodology 2018. Takeda ATM Submission 2018.
- The charts show the different weights of the indicators for each category. They do not show Takeda's performance, but an interpretation of the weights according to ATM Index methodology.
- The Red blocks show access initiatives developed by Takeda Vaccines that may have had some impact in the overall Takeda ranking*
- The blue blocks tag indicators with Takeda Vaccines' initiatives that, may not impact the overall ranking since Takeda global has already multiple initiatives on those indicators*
- Those indicators without color are areas with no initiatives by Takeda Vaccines*

LIST OF INDICATORS EVALUATED

General access to medicines management		
	Commitments	
		Governance
		ATM strategy
	Transparency	
		Managing for ATM outcomes: public reporting
		Stakeholder engagement
	Performance	
		Managing for ATM outcomes: performance management system
		Stakeholder engagement
		Governance
	Innovation	
		Innovation in business models
		innovation in governance and stakeholder engagement
Market influence		
	Commitments	

* Since this is a qualitative evaluation based on the data submitted by Takeda, this interpretation may differ slightly from the ATM Index evaluators

	Governance of ethical marketing
	Governance of anti-corruption
Transparency	
	Market influence: Policy positions
	Market influence: Memberships
	Disclosure of marketing strategy and practice
	Ethical marketing and corruption: disclosure of breaches
Performance	
	Ethical marketing and anti-corruption: incidence of breaches
	Ethical marketing and anti-corruption: Enforcement
	Compliance: Internal control framework
Innovation	
	Innovation in market influence and compliance
Research and development	
commitments	
	Product development: R&D commitment and strategy
	Planning for access: structured process
	Clinical trial conduct: Policies and compliance systems
	Clinical trial conduct: Post-trial access
Transparency	
	Disclosure of resources dedicated to R&D
Performance	
	Resources dedicated to R&D
	R&D pipeline
	High priority R&D
	Collaborative R&D: Share of pipeline
	Product development: Movement through the pipeline
	Planning for access: Project-specific plans
	Clinical trial conduct: Breaches
Innovation	
	Innovation in R&D
Pricing, Manufacturing and Distribution	
commitments	
	Commitment to equitable pricing
	Filing for marketing approval/registration targets
Transparency	
	Equitable pricing strategies: volume of sales disclosure
	Equitable pricing strategies: Price disclosure
	Public disclosure of registration status
Performance	
	Equitable pricing strategies: market and product scope
	Equitable pricing strategies: inter-country
	Equitable pricing strategies: intra-country
	Filing for marketing approval/registration: Needs-based

		Drug recall system
		Brochure and packaging adaptation: rationale use
		Aligning supply and demand
	Innovation	
		Innovation in Pricing, Manufacturing and Distribution
Patents & Licensing		
	Commitments	
		Patent filing and enforcement
	Transparency	
		Endorsement of TRIPS flexibilities
		Patent disclosure
		Disclosure of licensing practice
	Performance	
		Licensing: scale
		IP sharing
		Access-oriented licensing
		Licensing: Geographic scope
		Anti-competitive behavior: Trade policy
		Anti-competitive behavior: No-IP
	Innovation	
		Innovation in Patents & Licensing
Capacity Building		
	Transparency	
		Pharmacovigilance: sharing safety data
		Supply chain management: Reporting falsified and substandard medicines
	Performance	
		Capacity building in manufacturing
		Capacity building in R&D
		Capacity building in supply chain management
		Capacity building in pharmacovigilance
		Health system strengthening
	Innovation	
		Innovation in Capacity Building
Product Donations		
	commitments	
		Ad-hoc donation programs
	Transparency	
		Transparency in product donation management
	Performance	
		Quality of product donations
		Scale of product donations

9.7 TPP MODIFICATION BY THE ADDITION OF ACCESS COMPONENTS

Different modifications of the TPP by the inclusion of access parameters. The horizontal integration (Figure 14) may be easier to implement since it requires less access commitment. The vertical integration (Figure 15) has a stronger potential to enable real change and access mindset into de product development.

Attribute	Target claims to achieve innovative product launch	Required	Minimum threshold w/o compromising innovative product	Competitive Benchmark/ Comments	Status
Efficacy					
Safety					
Administration					
Patient / economic outcomes					
Other critical atributes					

Figure 13. Standard TPP. Attributes and characteristics assigned to each. Source: Takeda Vaccines

Attribute	Target claims to achieve innovative product launch	Required	Minimum threshold w/o compromising innovative product	Competitive Benchmark/ Comments	Status
Efficacy					
Safety					
Administration					
Patient / economic outcomes					
Other critical atributes					
ACCESS: CRITICAL CONSIDERATIONS					

Figure 14. Modified TPP: Addition of access as one more attribute to be defined. Moderate impact. Source: Author's own

Attribute	Target claims to achieve innovative product launch	Required	Minimum threshold w/o compromising innovative product	Competitive Benchmark/ Comments	**ACCESS IMPLICATIONS**	Status
Efficacy						
Safety						
Administration						
Patient / economic outcomes						
Other critical atributes						

Figure 15. Modified TPP: Access as one characteristic that needs to be addressed by each of the attributes of the TPP. High impact Source: Author's own