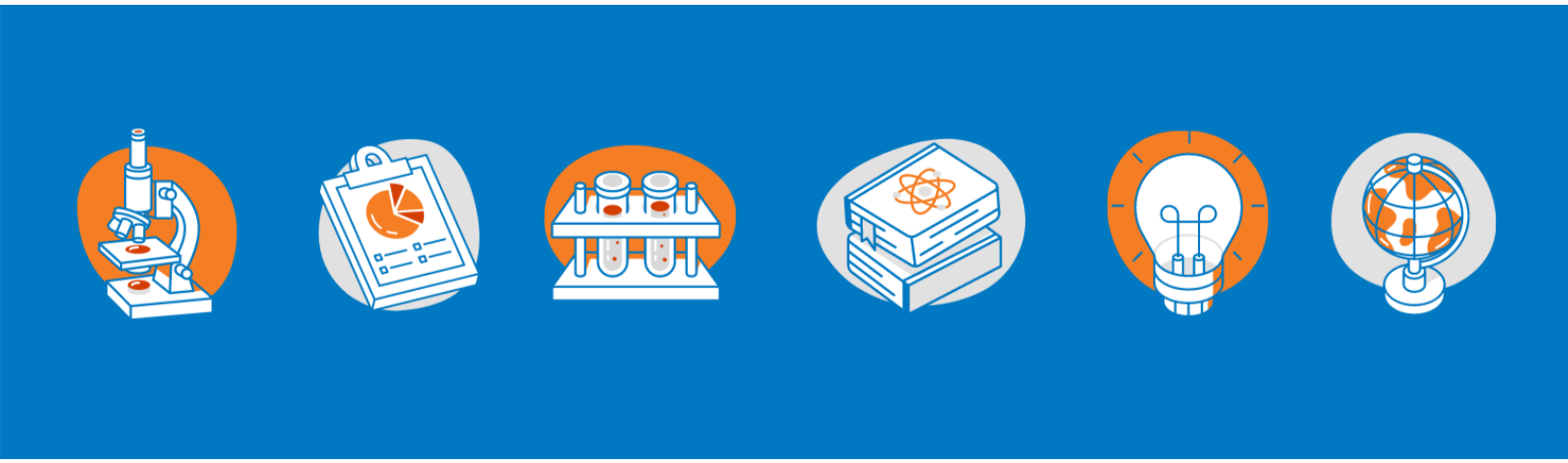

STUDY REPORT

A Framework for Action to Support Quebec's Biopharmaceutical Innovations and Bolster Quebec's Autonomy

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Table of contents

Context

Quebec has a rich history and vibrant tradition of biopharmaceutical research and development. The discovery and development of these innovations have been firmly nurtured by a particularly favourable business environment and sound economic policies, features which have predominantly been the purview of the Quebec government.

This willingness to support these innovations is still very strong, most notably within the Quebec Life Sciences Strategy, a component of which is the biopharmaceutical sector.

The biopharmaceutical industry has undergone extensive changes over the decades. As a result, the political, regulatory, and economic environment in which it operates no longer provides the sector with the support it needs to develop to its full potential and make Quebec one of the industry's key stakeholders, both here and internationally.

Integrating these innovations into the Quebec healthcare system is a vital step for a life sciences company. It allows companies to test their innovations' behaviour in a real healthcare setting and, as a result, facilitates the foreign market integration process. Therefore, close collaboration between economic and health ministries has now become imperative to ensure life sciences companies' success.

Many of these innovations have experienced significant challenges when integrating into the Quebec healthcare system, especially the public prescription drug insurance plan. In some cases, Quebec-based innovations received negative responses to reimbursement requests in Quebec even though they were accepted in other provinces.

These constraints have created a perception among Quebec researchers and entrepreneurs that their efforts and contributions are not adequately recognized and supported. As Quebec's largest biotechnology and life sciences network, BIOQuébec is alarmed by these concerns, given that its mission is to foster this industry's growth and support its contribution to creating wealth, promoting Quebec's involvement, and improving everyone's health and quality of life.

THE STUDY

SCOPE OF THE STUDY

BIOQuébec commissioned The JBL Group to produce a comprehensive account of the situation by **first, rigorously documenting** the Quebec healthcare system's recommendation process for Quebec-based innovations and **secondly, to develop**, with industry partners, **public policy proposals** that would support the Quebec biopharmaceutical industry's innovations and development.

BIOQuébec's review was prompted by a widespread perception among many members that Quebec-based drugs and biopharmaceutical industry products were unfavourably considered by the Quebec health and social services network.

Before looking at possible courses of action, it was important to be able to not only document this malaise, but also assess and measure how Quebec-based drugs are being treated. The goal was to verify whether these perceptions are based on facts, and if not, to determine the factors that have created the malaise.

To better formulate the recommendations and make them more evidence-based, the report analyzed in detail how biopharmaceutical innovations, when at the recommendation stage in the Quebec healthcare system, were handled by the provincial network.

We present herein the result of this process. After an analysis of how biopharmaceutical innovations are received, approved, and recognized in Quebec and elsewhere in Canada, we will offer several possible solutions, grouped into two categories:

1. Intervention strategies that will enable all innovations to better integrate into the Quebec healthcare system, thus reducing the disparity with Canada's other provinces; and
2. Intervention strategies that will allow Quebec-based innovations to have a greater chance of evolving with specific support throughout the innovation process, which will enable the biopharmaceutical industry to reach its full potential and maximize its activities' benefits for Quebec's population and economy.

The report will suggest clear intervention strategies so that public policies can meet these objectives.

These proposals will be designed in a way that supports and strengthens the government's economic approach as defined in its document titled *Une vision économique ambitieuse, un Québec qui gagne* (an ambitious economic vision, a successful Quebec) and in the new Québec Research and Innovation Strategy.

THE METHOD

JBL used a methodical, three-stage approach: first, identifying Quebec-based molecules; second, comparing the consideration given to Quebec-based molecules in Quebec and in Canada's other provinces; and third, comparing the consideration given to all molecules, regardless of their origin, in Quebec and elsewhere in Canada.

Identifying Quebec-Based Innovations

In the first stage, we used an accepted and validated definition of a pharmaceutical innovation: new patented drugs submitted to Health Canada for approval and accessible through Health Canada's Register of Innovative Drugs, which specifies the molecule's name, its brand name, the name of the manufacturer, and the date of the notice of compliance. This register is available online on Health Canada's website, and as of July 31, 2020, it listed 414 molecules for the period from 2006 to 2020.

Our discussions with representatives from BIOQuébec, scientific community stakeholders, and academic specialists led us to our second stage: adopting a very broad definition of what constitutes a Quebec-based pharmaceutical innovation, for methodological reasons, to ensure that we had a sufficiently large sample to allow for comparisons and to take into account the complex nature of this industry, whose development is not linear.

We defined Quebec-based molecules as those that either held a patent that can be qualified as Quebec-based because of its holders' origins, or that met two of the following three criteria: Quebec preclinical sites/centres located in Quebec, clinical sites/centres located in Quebec, head office located in Quebec.

However, it is worth noting that in some cases, the contributions of Quebec centres and researchers to preclinical or clinical research were minor. Therefore, even though these molecules were classified as Quebec-based as per our research criteria, the extent of their designation as being "Quebec-based" could be limited.

We want to point out that collecting this data required extensive research, which was even more difficult because the subject had not yet been studied. **There is no register, compilation, or directory of Quebec-based biopharmaceutical innovations.** To address this significant challenge, university researchers have initiated a process to create a database, but it remains at the project stage for the time being.

The work we have done to create this compilation is the first contribution towards collecting important data for this sector's development. This methodical approach made it possible to identify seventy molecules that can be considered as being Quebec-based according to the very broad definition being used.

Assessing Quebec-Based Innovations

The second stage of our research involved examining, for each of these molecules, the notices issued by the assessment bodies, namely the *Institut national d'excellence en santé et services sociaux (INESSS)* for Quebec, and the Canadian Agency for Drugs and Technologies in Health (CADTH) for Canada's other provinces. Once again, it is important to mention that establishing this compilation required an extensive review process.

Out of a total of 70 molecules, 53 were assessed by both the CADTH and the INESSS. These were the ones selected for analysis because a comparison can be made of the decisions rendered by the assessment agencies. These 53 molecules generated 84 separate submissions, because several products may have required assessment for more than one therapeutic use.

Here are the details of this comparison:

- Out of the 84 submissions, 57 notices by the INESSS and the CADTH were similar, with 44 recommendation notices and 13 rejections.
- For the 27 other submissions, the notices were different. In 32.1% of cases - nearly one third - the two agencies, who make their decisions based on a scientific process, came to differing conclusions for issuing a recommendation or a rejection notice for a drug.
- In 9 of the 27 cases, the INESSS issued recommendation notices whereas the CADTH issued rejections.
- In 18 of the 27 cases, the CADTH issued recommendation notices and the INESSS issued rejections.
- This means that in 67% of the 26 cases where the two agencies issued opposing notices, the CADTH's issued a recommendation, with the INESSS only issuing recommendations in 33% of the cases. **In other words, when there was a difference of opinion, the INESSS was the more restrictive in accepting a drug, two out of three times.**

Without further analysis, this compilation could suggest that Quebec-based drugs receive less favorable assessments in Quebec than in Canada's other provinces. This would too quickly lead to the conclusion that they are victims of a negative bias by Quebec regulatory authorities. But before reaching such a conclusion, it is important to first look at how these notices compare to those for all drugs, regardless of their origin.

Assessing All Molecules

For these reasons, we performed cross-checks using another database, a compilation maintained by The JBL Group, containing all the recommendations made by the INESSS and the CADTH from 2016 to the end of 2020, regardless of the molecule's origin.

This compilation consists of 296 notices involving 241 molecules. Of these 241, notices were issued by both agencies in 216 cases.

- Out of 216 notices issued by the INESSS and the CADTH, 153 were similar.
- In 63 of the cases, the two agencies issued different recommendations, which is 29.2% of the total. This opposite rate of recommendations is quite close to the 32.1% found in the above-mentioned analysis on the assessment of 70 Quebec-based molecules.
- Among these opposite recommendations, the INESSS issued recommendations and the CADTH issued rejections in 8 of the cases.
- In 55 cases, the INESSS issued rejection notices, whereas the CADTH issued recommendations.
- When there was a difference of opinion, the INESSS was more restrictive 7 times out of 8.
- **When looking at the 216 molecules studied, the INESSS issued 129 recommendation notices representing a 59.9% acceptance rate and a 40.1% rejection rate. The CADTH issued 176 recommendation notices representing an 81.5% acceptance rate and an 18.5% rejection rate.**

Finding: Innovations are less integrated in Quebec

No specific consideration, either positive or negative, for Quebec-based drugs is discernible in the INESSS notices. Overall, the molecules that can be described as being Quebec-based are assessed the same way by the INESSS as those of all other origins.

What is significant, however, is that overall, there are fewer recommendation notices for molecule registration in Quebec through the INESSS, than there are in Canada's other provinces with the CADTH.

For all molecules assessed between 2016 and 2020 by both agencies, INESSS' rejection rate was 40.1% whereas the CADTH's was 18.5%. T**he INESSS is a stricter assessment agency than the CADTH.**

The analysis also showed that even though both agencies issued recommendation notices, in several cases the process leading to a recommendation notice by the INESSS was more arduous due to the number of submissions that the manufacturer sometimes had to produce - two, three and even four - or because of the time it took to issue a notice. From the biopharmaceutical industry's perspective, these various findings suggest that regardless of the merits of the notices produced by these assessment agencies, **the Quebec assessment system may be less welcoming and more restrictive than the one for Canada's other provinces**.

This negative impact is partially mitigated by the use of a concept specific to Quebec, that of the "patient of exception", which allows the public drug insurance plan to cover drugs that have not been the subject of a recommendation by the INESSS and that are not listed on the "plan's drug list". This concept provides a loophole and allows patients to benefit from drugs they would not have access to through standard approval procedures.

By and large, our research indicates that the perception of many Quebec biopharmaceutical industry representatives of negative bias is not due to them receiving unfavourable consideration, but rather to an INESSS' more stringent approach to assessing drugs for all innovations.

POTENTIAL SOLUTIONS

While our research has measured and documented the unequal treatment of innovations in Quebec compared to other Canadian provinces, it has also brought to light the many obstacles that hinder the development of Quebec-based innovations and various shortcomings in support mechanisms. In the second part of this report, we offer two sets of potential solutions. The first addresses ways to overcome the unequal treatment factor, while the second addresses policies to support Quebec-based innovations.

POTENTIAL SOLUTIONS TO COMBAT INEQUITABLE CONSIDERATION

Our research highlighted an element that is distinct to Quebec's regulatory and administrative system pertaining to drugs. The INESSS is more restrictive in its recommendations on reimbursement than the CADTH, which advises the other nine Canadian provinces.

Not providing recommendation notices for reimbursing a drug to such a high number of applications has a negative effect on the biopharmaceutical companies receiving the rejection notice. It also impacts those more experienced biopharmaceutical companies that are at the stage where they can submit molecules for assessment. But **this inequitable consideration**, documented in the previous pages, **also has a negative effect on the entire industry**, for Quebec companies and for foreign companies doing business in Quebec, including small biopharmaceutical companies, research centres, and the academic sector, **by creating a climate that is less conducive to innovation and by affecting Quebec's appeal.**

It is important to note that the INESSS is not the only agency involved in the drug assessment and approval process. The Canadian system is complex and involves many agencies, mainly because each province and territory has its own healthcare system. First, Health Canada assesses the quality, safety, and effectiveness of drugs. Second, the CADTH or the INESSS provides its assessment. Then, the pan-Canadian Pharmaceutical Alliance negotiates with the pharmaceutical companies on behalf of the provinces to determine a price for the drug. Finally, each province must list these drugs for reimbursement. Constraints or obstacles can be encountered at each of these steps.

The report looks at the INESSS - rather than the system's other components - because it is the assessment system's first point of contact for those Quebec innovators who are BIOQuébec members. Moreover, since the report's initial purpose was to compare the Quebec environment

with the Canadian environment, naturally the report's focus would be on the INESSS, which is the main element that differentiates Quebec from the rest of Canada.

The very fact that Quebec healthcare authorities decline to reimburse innovative drugs more often than those in Canada's other provinces can clearly create the perception that Quebec is less open to drugs and therapeutic innovation and, as a result, is a less advantageous base of activity. This may affect Quebec's efforts to present itself as an attractive location for investments and biopharmaceutical research. This less favourable image can also affect the development opportunities for Quebec professionals and researchers and weaken the ecosystem on which Quebec businesses must be able to rely. Furthermore, the fact that Quebec-based innovations, for whatever reasons - and even if it is not due to a negative bias - may encounter more obstacles in accessing the market in Quebec than in Canada's other provinces, sends an extremely negative message that is not conducive to the ecosystem's development. The adage "no one is a prophet in their own land" does not guarantee success in economics.

It is difficult to start thinking about supporting biopharmaceutical research and the development of Quebec-based drugs without addressing this issue.

The results of our research and our consultations with industry stakeholders indicate that it is preferable to demand that Quebec companies and Canadian and foreign companies operating in Quebec **be able to compete on what can be described as a level playing field**, so that a molecule can be entitled to the same consideration in Quebec that it would receive elsewhere in Canada and, for the most part, in other countries. This would correct what is, in many respects, an anomaly.

The objective is to ensure that biopharmaceutical companies are not subject to unequal treatment because of Quebec regulatory authorities' stricter recommendations that those in Canada's other provinces.

It is important to keep in mind that this higher number of rejections also impacts those for whom healthcare policies are designed: the citizens who use and benefit from them. **Drug reimbursement rejections or longer approval times than elsewhere can deprive patients of therapeutic approaches that could improve their health or prolong their life.**

The longer this situation lasts, the worse it will get. In fact, the cost-benefit analysis of any innovation being assessed is done based on those of other more recent innovations, which obtained their recommendation notice before the criteria were narrowed a few years ago. Over time, with fewer and fewer innovations entering the system, assessment agencies will only be able to perform their cost-benefit analyses using technologies which are becoming increasingly outdated. As such, the gap between innovation and the comparative standard of treatment will be wider, which will increase the chances of rejection notices and make receiving financial burden relief less and less realistic.

A THORNY DEBATE

To ensure that the drug reimbursement assessment mechanisms in Quebec are similar to those in Canada's other provinces, changes would need to be made to the INESSS' practices or assessment criteria. **BIOQuébec believes that this sensitive issue can be raised in a respectful and constructive manner.**

First, by very clearly stating the principles upon which the drug and biopharmaceutical industries' policies should be based, such as that, under no circumstances, are economic decisions which compromise the quality of care or the safety or health of citizens to be made.

Second, **by acknowledging the tremendous contribution made by the INESSS**. Nobody disputes this well-respected agency's thoroughness or its employees' expertise. Rather, our questions are systemic in nature and apply to its mandate's structure and its positioning within the drug ecosystem.

The INESSS' responsibilities go far beyond drugs. Established in 2011, this agency is the product of the merger of the *Conseil du médicament* and *the Agence d'évaluation des technologies et des modes d'intervention en santé*. Its mission is to promote clinical excellence and the efficient use of resources across the entire health and social services network. It has three branches: the department responsible for assessing drugs and technologies represents less than a third of its workforce.

Generally speaking, in its other scopes of activity, the INESSS' analyses, assessments, and recommendations on best practices focus on elements specific to the Quebec health and social services network or which directly involve Quebec stakeholders. For example, in its most recent publications (October 2021), the INESSS studied the needs of families followed by the Integrated Perinatal and Early Childhood Services and on creating and identifying a cohort of Quebec lung cancer patients. It also continues to monitor the COVID-19 pandemic's evolution by assessing hospitalization risks and projecting hospitals' needs.

However, drugs are a universal domain, without borders, where molecules from all over the world are also used in other industrialized societies to which we can compare ourselves. As far as drugs are concerned, the rules governing their approval - safety, efficacy, clinical benefits, etc. - are exactly the same as those in other nations with comparable standards. As such, there are few, if any, characteristics specific to Quebec that would justify the province having an independent assessment mechanism when a similar mechanism already exists for Canada's other provinces. For example, European Union member countries have delegated this responsibility to the European Medicines Agency.

However, we understand why Quebec has created assessment mechanisms that could be perceived as duplicates. Above all, it is a political choice: the Quebec government's desire to

protect the provinces' constitutional jurisdiction over healthcare and protect or preserve Quebec's independence from federal or interprovincial decision-making processes.

Quebec's specificity has real consequences. The CADTH, which is the INESSS' federal counterpart, issues notices for all other provinces and territories without having any ties to their various healthcare systems. Although its status guarantees its independence from the government, the INESSS does experience organic connections with the Quebec healthcare network. These ties mean that, when assessing a drug's efficiency and the budgetary burden it creates, the INESSS will naturally tend to internalize the constraints of Quebec's government. These concerns are all the more prevalent since Quebec is the only province with a universal drug insurance plan to which the government makes a substantial contribution and upon which reimbursement approvals can have a greater budgetary impact.

These particular characteristics of the INESSS highlight the fact that when assessing drugs, this agency does not have the primary function of acting as a safeguard to ensure that citizens' health and safety is protected, a role that Health Canada already plays. Its main role is that of gatekeeper so the payer, in this case the Quebec government, can control costs and make efficient and optimal use of public resources. **So, when it comes to drugs, the INESSS' primary role is to protect pharmacoeconomic and budgetary interests.**

For this reason, BIOQuébec's proposals are not intended to pit an economic perspective against a social or healthcare one, but rather to suggest a modification to the economic perspective that is already the foundation of the INESSS' approach. When viewed as such, it is not at all inappropriate to use economic arguments when recommending changes to its practices.

This conversation is even more appropriate given that drug assessment processes are evolving, as the INESSS acknowledges that substantial changes have occurred in the legislative and political environment regarding the development, assessment, and optimal use of drugs in Quebec and Canada. These changes include the Quebec government's adoption of the 2017-2027 Quebec Life Sciences Strategy and its membership in the pan-Canadian Pharmaceutical Alliance. More recently, a coordinated assessment process between Health Canada and technology assessment agencies such as the CADTH and the INESSS has been implemented to decrease the time between a Notice of Compliance issuance and listing recommendations. Additional changes may be brought further to ongoing work at Health Canada, the CADTH, and the Patented Medicine Prices Review Board. All these elements create new challenges in drug assessment, requiring a different way of fulfilling this mandate.

It is in this same spirit that **BIOQuébec is suggesting four courses of action that would have the effect of modifying the INESSS' practices;** modifying some of the criteria upon which it bases its decisions; eventually modifying some of the wording of the INESSS' founding legislation; and potentially modifying the relationship between the INESSS and the government.

These suggestions are also in line with the Quebec government's efforts to simplify government action, to reduce administrative obstacles that can hinder the development and fluidity of interactions between the State and its constituents or negatively affect services to citizens.

01 Increasing Transparency and Collaboration

The first element that needs to be considered is the process, namely the INESSS' methodology: it operates in a manner similar to that of a quasi-tribunal, where interactions between the regulator and the companies submitting applications are rigid and kept to a minimum. The company simply submits an application for a molecule to be approved, and after a certain time, the agency issues a notice which cannot be appealed.

By comparison, the CADTH's model is based more on principles of transparency and collaboration. Once the CADTH assessors have completed their preliminary assessment of a drug, they submit their report to the stakeholders and the company that submitted the application for comments and possible changes, before forwarding their conclusions to the panel of experts that will make the final decision. **This type of mechanism allows for flexibility and transparency and replaces adversarial relationships through a collaborative and interactive approach.**

Another way to introduce flexibility into the process is to **reduce the time frame for rejections**. The CADTH allows for appeals in certain cases, whereas the INESSS does not have an appeal mechanism. Rather, a company that has received a rejection must submit a new application. This represents significant delays: several months before notification is made that the application has been filed and then six months before the recommendation or rejection is issued. Furthermore, the manufacturer also must submit new elements for its application to be admissible. As there are costs associated with these steps, these constraints – involving time and money - sometimes lead to the company opting not to submit a new application. Introducing an appeal mechanism could help to add a degree of flexibility to INESSS' process.

Finally, it would be appropriate to **introduce a mechanism for analyzing cases** for which the INESSS has issued a rejection notice for a drug, yet the CADTH has issued a recommendation, and vice versa. In the interest of benchmarking, such a mechanism would lead to a better understanding of the criteria and reasons that led the INESSS to larger numbers of rejection notices, and perhaps put pressure on the Quebec agency by requiring it to shoulder the burden of proof to a certain degree.

Legal Rigidity

The INESSS also differs from the CADTH in that it uses a criterion for the therapeutic value of a drug that the CADTH does not. The application of this criterion has led to several rejection notices that differentiate the Quebec agency from the pan-Canadian agency.

The INESSS' decision-making process is set out in an act, 2010's *Act respecting the Institut national d'excellence en santé et services sociaux*. This law outlines the parameters that the INESSS must follow in its recommendations on the use of a drug. Section 7 of the law specifies these criteria:

> In exercising the functions described in paragraph 8 of section 5, the institute must first assess the therapeutic value of a medication. If this is not established to its satisfaction, the institute sends a notice to that effect to the Minister.
>
> If the institute considers that the therapeutic value of a medication has been established, it sends its recommendation to the Minister after assessing
>
> (1) the reasonableness of the price charged
>
> (2) the cost-effectiveness ratio of the medication
>
> (3) the impact that entering the medication on the list will have on the health of the general public and on the other components of the health and social services system, and
>
> (4) the advisability of entering the medication on the list, given the purpose of the basic prescription drug insurance plan.

It is surprising that the criteria the assessment body must use are written into a law. This provision does not exist elsewhere in Canada because the corresponding institution, the CADTH, is an independent body that does not fall under the jurisdiction of the provinces that use its notices and has not been the subject of a legislative proposal.

The second of the INESSS' distinguishing features is the unambiguous statement in the legislation stating that "the institute must first assess the therapeutic value of a medication. If this is not established to its satisfaction, the institute sends a notice to that effect to the Minister." This criterion does not apply to the CADTH, which focuses its health technology assessments on clinical effectiveness and cost-effectiveness, meaning the CADTH guidelines focus on costs and outcomes.

The introduction of a therapeutic value analysis before taking into account the economic factors resulting from its use (price, cost-effectiveness, financial impact on the system) introduces an element of uncertainty and contributes to the higher number of rejection notices by the INESSS because the assessment of therapeutic value is not an exact science and may be altered by differing interpretations.

However, since this is a law that expresses, in general terms, the criteria to be used, the real issue will be the regulatory agency's interpretation of these rules. More specifically, the INESSS has developed a concept for interpreting therapeutic value, that of "added value," which is not found elsewhere in Canada. In many cases, this criterion's application also helps to explain why a drug is reimbursed elsewhere in Canada, but not in Quebec.

An INESSS document titled *Évaluation des médicaments aux fins d'inscription, évolution des modalités* (assessing drugs for listing purposes, a changing approach), describes the concept as follows (unofficial translation): The INESSS first determines if the drug has therapeutic value. If it is recognized as having such value, it is said to be an **added** value if the drug offers an additional objective benefit in terms of its efficacy, its safety profile, the patient's quality of life or its therapeutic advantages relative to comparable treatments. It may be considered low, moderate, or high, depending on the significance of the results and on their degree of uncertainty. It is said to be **similar** if the drug does not offer any additional benefit relative to its comparators.

One implication of using this concept is that it can have two consequences. On the one hand, determining what constitutes "added" therapeutic value may be subject to interpretation and may involve an arbitrary element that could lead to inconsistent assessments. On the other hand, assessing a case in which the therapeutic value is viewed as "similar" may lead the INESSS to reject a drug or refuse to analyze it if it does not meet the only criterion that will then be used: the cost of the drug versus that of its comparators.

In addition to restricting access to the Quebec market, this can hinder innovation by limiting new products' arrival on the market. While the INESSS doesn't consider these products as having added value, they can introduce competition into the system, lead to other therapeutic applications, and contribute to the innovation process.

For these reasons, **it would be appropriate for the INESSS to perform a more comprehensive review of this therapeutic value criterion: particular attention should be focused on its "added" and "similar" therapeutic value components.**

More generally, a review of the Act and its relevance as a tool and action guide outlining the responsibilities attributable to the life sciences industry, the economy, and public finances could also be appropriate. Unfortunately, an Act introduces an element of inflexibility into operations that must evolve at the same pace as science. The one that regulates the INESSS' obligations is almost 12 years old, and we believe it needs to be updated.

ADMINISTRATIVE RIGIDITY

While companies must deal with the legal inflexibility described above, the criteria set out in the legislation are less specific than the CADTH's administrative criteria. However, the INESSS has more rigid administrative criteria than the CADTH, although its administrative nature allows for easier adaptability.

Another factor in the weighty and inconsistent nature of the decisions is that, paradoxically, they are based on the fact that the INESSS' procedures and the criteria it uses are much less detailed than those used by the CADTH. As such, decisions made by the INESSS are more frequently based on its interpretation of the generally-described rules.

The process could also be facilitated and streamlined in cases where the rejections result from the INESSS' more stringent scientific evidence requirements than those used by the CADTH. For example, the INESSS requires that the manufacturer submit randomized double-blind studies, usually Phase III, that have been accepted for publication to even consider assessing an innovation.

Increasingly, data to validate the safety and efficacy of innovative treatments is being generated faster than ever; the introduction of artificial intelligence tools to accelerate their analyses allows innovative companies to expedite the development of these treatments and do so in unconventional ways. As such, the rigidity of assessment processes has become a significant obstacle that creates unjustified delays caused by regulatory authorities that are frequently uncomfortable with this rapid development. **Therefore, it would be imperative that assessment mechanisms be more flexible and adaptable as science evolves, mainly to adjust to the acceleration of research and innovation**.

Our research indicated that in several cases, even though both agencies issued recommendation notices, the process leading to a recommendation notice by the INESSS was more arduous due to the number of submissions that the manufacturer sometimes had to produce - two, three and even four - or to the time it took to issue a notice. From the biopharmaceutical industry's perspective, these various findings suggest that regardless of the merits of these assessment agencies' notices, the Quebec assessment system may be less welcoming and more restrictive than the one for Canada's other provinces.

However, BIOQuébec has noted that INESSS has made tremendous progress in reducing the time required to issue a notice. It also welcomes the fact that the INESSS has adopted the practice of initiating the review of a drug after having assessed its efficacy, safety, and quality but before Health Canada has authorized it, which serves to shorten delays. Finally, it welcomes the considerable efforts the INESSS has made to adapt and align its practices with the pharmaceutical industry's increasing complexity and fast pace of innovation and development.

UNNECESSARY DELAYS CAUSED BY AN INCOHERENT PROCESS

Although the INESSS is responsible for assessing and making recommendations to the Minister on listing a drug, listing agreements are negotiated within the Ministry of Health and Social Services. This rigidity, especially the administrative one described above, means that some innovations do not meet the INESSS' assessment standards.

The introduction of a new drug can save lives or improve patients' health. The time factor must be considered, particularly for rare diseases, serious chronic diseases, and oncology treatments. The consequences of avoidable delays can be dangerous for patients affected by these diseases. Therefore, one of the healthcare system's goals should be to ensure that new drugs that can make a big difference in treating a disease can be accessible to patients as quickly as possible.

A recent example seems to indicate that this concern for speed does not appear to be among Quebec's priorities. On October 20, 2021, Quebec approved the reimbursement of a costly gene therapy drug, Zolgensma, used to treat spinal muscular atrophy. Health Canada approved this drug in December 2020. Ontario announced its use in early January 2021 by granting an exception to make the drug available before the price negotiation process between the manufacturer (Novartis) and the pan-Canadian Pharmaceutical Alliance had been completed. Quebec waited for the negotiation's results to announce that it would reimburse the drug, which was an additional ten-month period, a time during which families waited for this life-changing treatment for their babies. **In this case, the delays were not attributable to the INESSS, which had issued a recommendation notice to the Minister as early as December 2020.** In fact, the Ministry of Health and Social Services' decision-making process is at fault. It is important to note that in this specific case, the drug's use as authorized by the INESSS is more restrictive than that of the other provinces. This means that Quebec babies, who were not in the age range accepted by the INESSS, were denied access to the drug but would have been eligible for it if they lived in Ontario.

Other jurisdictions use a different approach and prioritize approval speed. For example, England's National Institute for Health and Care Excellence (NICE), which is somewhat of a hybrid between the CADTH and the INESSS, proudly states: "*We're changing how we assess new drugs, devices, diagnostics and digital technologies to provide faster and fairer access in the NHS. The changes will also improve the way we work with patients, the NHS and the life sciences industry.*"

In addition to fostering patients' well-being, reducing delays in assessment processes also supports research and innovation in a globalized scientific and technical environment in which research and discovery cycles are accelerating.

The Minister's role should therefore be redefined within this new context: while it should be performed with restraint and can be justified by the fact that, once the therapeutic value of a drug has been assessed and recognized by the INESSS, notices issued by the organization are based on economic criteria, such as efficiency, fiscal impact, and equity in relation to other uses of public funds.

These issues are related to the sustainability of public finances, budgetary choices, and the trade-offs between needs. By definition, they are the responsibility of the government and its ministers. The minister and the government are the ones that can decide on the trade-offs pertaining to the optimal use of healthcare resources and other objectives, such as support for innovation or economic development.

For these reasons, the Minister's involvement can, in some cases, introduce a degree of flexibility into rigid decision-making processes. It can also serve to present factors related to social acceptability or the awareness of issues that elected officials, who represent the citizens, are better able to integrate into decision-making processes.

POTENTIAL SOLUTIONS TO SUPPORT QUEBEC INNOVATIONS

Quebec invests considerable resources to support innovation in the life sciences and biopharmaceutical sector, as evidenced by the efforts made through the Quebec Life Sciences Strategy, which aims to attract billions of dollars in private investment and position Quebec as one of the five North American hubs. Four projects launched by the Government of Quebec are working on updating this strategy.

The strategic document published in November of 2021, *Une vision économique ambitieuse, un Québec qui gagne*, points out that, along with aerospace and aluminum, life sciences are one of the three strategic, high added-value sectors that the Quebec government intends to support through four areas of focus: increasing investments in research and innovation in the life sciences, namely through clinical research; boost local industry by creating innovative businesses; attract new investments; further integrate innovation into the health and social services system.

However, there are gaps in the continuum of measures for biopharmaceutical companies. Current funding measures are adequate, but they can always be improved - BIOQuébec made specific recommendations to this effect in a previous report. However, especially at the beginning stage of the innovation process, support mechanisms are largely absent downstream, i.e., in the more advanced phases of the innovation process and at market access time. For example, in the Québec Life Sciences Strategy, while the issue of market access is addressed, it is not treated as a priority.

To ensure that Quebec has dynamic and innovative industry that is also able to develop to its full potential, the government will need to increase its support for Quebec-based biopharmaceutical innovation and revisit its policies.

It is worth noting that life sciences are an exception because, for most government-supported industries, guidance and support are not limited to research or financing, but continue until the economic activity is complete, i.e., sales, marketing, and exportation. According to the Organisation for Economic Co-operation and Development's definition, innovation is not just an idea or what results from research. Innovation is also when the idea is transformed into action and translates into economic activity.

Developing more proactive policies in favour of Quebec-based biopharmaceutical innovations will lead, in some cases, to them enjoying preferential treatment. The idea of preferential treatment is not inconsistent with the "level playing field" principle suggested above and, to a certain degree, is an extension of it.

The two policies do not target the same stakeholders. Fair processing of drugs focuses on more mature companies at the stage where their drug has been approved by Health Canada and only now requires its reimbursement to be authorized. Support for Quebec-based innovations targets small companies or innovations that aren't at the stage where their research is ready for market. The first case supports drugs available now, whereas the second one supports drugs not yet available.

A FAVOURABLE CONTEXT

The current context is favourable to such a process, namely because the COVID-19 pandemic has created a paradigm shift.

By altering demand, limiting cross-border movement, and disrupting supply chains, the pandemic has highlighted Quebec and the other provinces of Canada's vulnerability in accessing essential goods and products. This was reflected across the healthcare sector's entire continuum of needs, from procedural masks to vaccine production capacity.

These disruptions led to the rise of a type of economic nationalism, here and elsewhere, which Premier François Legault defines as assertive economic nationalism. It has been applied in Quebec through the "blue basket" concept, whereby the Quebec government encourages citizens, businesses, and public agencies to purchase Quebec-made products and promotes efforts to support substituting imported products with local ones. He reiterated this goal in his opening speech in October of 2021. These are all expressions of genuine economic nationalism, which seeks to promote the local economy and local producers.

This approach to economic development can and should be applied to the biopharmaceutical sector. The most acute shortages were experienced by the healthcare sector, which led to this protectionist reaction. The hope is that the biopharmaceutical industry can benefit from this movement.

The government's economic strategy document points out that the battle against COVID-19 has also shown the importance of having drug and vaccine production facilities on our territory. Quebec can achieve this using an important asset: a diverse and integrated life sciences sector that includes high-level human resources, significant research capabilities, and efficient operational production units.

One of the most powerful development tools available to governments is the implementation of public expenditure and procurement policies. Again, it is an anomaly that this powerful tool is not being used to support the development of biopharmaceutical innovations, given that more than 40% of the Quebec government's budget is allocated to health.

It would make sense for Quebec to apply the spirit of policies designed to promote buying Quebec-based products to biopharmaceutical innovations. The recommendation is that financial, political, or regulatory measures be developed to give preferential treatment to Quebec-based innovations.

But clearly, domestic production support cannot be applied to biopharmaceutical activities across the board. Such efforts would be hampered by the unique nature of this industry and the products it provides, which are for human health.

While the concept of preferential treatment is easy to support, its implementation still poses a number of challenges.

SPECIFICITIES TO CONSIDER

The first obstacle is that the regulation of drugs designed for human health cannot tolerate any form of compromise: this excludes favouring a medicine because of its Quebec-based origin even if other drugs are more appropriate. By definition, any and all situations where preferential treatment could directly or indirectly affect patient safety and compromise efforts to improve their health must be avoided.

The second obstacle is that international trade rules are designed to prevent countries from providing their industries with support that would constitute unfair practices for foreign competitors. Any form of support to an industry must follow these rules, either by adhering strictly to them or finding ways to develop forms of support that will pass the test of international

agreements to which Canada is a party and which apply to provincial governments. However, it is important to understand that the art of international trade is based on a delicate balance between each country's condemnation of the impediments to international trade that it may face and its initiatives to protect its own industries. Many examples of economic nationalism and protectionism run counter to international rules, such as the Buy America Act, Europe's railway industry practices, and the food industry's application of health standards.

The pandemic has clearly shown that the biopharmaceutical industry, even though it is globalized, has very deep national roots and is not an industry without borders. The production and distribution of vaccines were largely dependent on companies' nationality and their production facilities' location.

The challenge will be to implement economic nationalism measures, defended by all companies, by judiciously using the State's levers. Theoretically, if specific support measures for Quebec's companies can create compliance issues regarding international trade rules, support measures for Quebec-based innovations could be more easily compatible, especially if they are accessible to all innovations that meet the definition criteria for Quebec-based innovations, regardless of the origin of the individuals, organizations or companies that develop them.

The third obstacle is that of fairness. In the name of economic nationalism, Quebec must take steps to support its own industry; it must also consider that foreign producers are often present in Quebec, and while they may be competitors, they are also partners. Many foreign pharmaceutical companies operate, to varying degrees, in Quebec, and their economic contribution is significant. They could consider support for Quebec-based innovations as being unfair.

This fear appears to be more theoretical than real, mainly because these two groups of companies generally do not operate on the same level. Foreign companies operating here are generally mature, have developed drugs approved by Health Canada and have marketing activities. Quebec's biopharmaceutical companies are more often at the research and development stage and therefore are not directly competing with mature foreign companies. Our research has shown that the number of molecules that can be broadly defined as Quebec-based is very small. Out of a total of 414 drugs in Health Canada's Register of Innovative Drugs, 70 could be described, directly or indirectly, as Quebec-based. But those that could be described as completely Quebec-based can be counted on the fingers of one hand. Therefore, the number of Quebec-based molecules that could potentially benefit from support would not only be very low, but most likely at a less advanced stage of development. Any assistance they would receive would not cause any market distortion.

PROMISING AVENUES OF INTERVENTION

In light of the factors that have just been mentioned, BIOQuébec suggests considering nine avenues of intervention that would help Quebec-based biopharmaceutical innovations while constructively and fruitfully supporting the Quebec government's economic development strategies.

01 Creating an Observatory

The first element of a strong policy to help Quebec-based biopharmaceutical innovations is being able to identify them. While this may seem obvious, our research showed - to our great surprise - that there is no database offering an inventory of Quebec-based innovations, no structured information system in government agencies such as the Ministry of Economy and Innovation or the healthcare network, nor a directory of companies that could be qualified as Quebec-based based on the extent of their presence.

It is very clear that if Quebec wants to create a policy to support Quebec-based biopharmaceutical innovations, it must be able to identify them to determine who is eligible for support measures and provide the necessary help.

Therefore, **BIOQuébec believes that creating an observatory for the Quebec biopharmaceutical industry is particularly important.**

This is not an easy task. The first step would be to use various criteria to define what constitutes a "Quebec-based" innovation. In our research, we used a very broad definition of this concept.

But when it comes to government support, a much more restrictive definition will certainly be required: significant involvement in creating, research, clinical trials, manufacturing, and marketing will be required. This type of support won't help biopharmaceutical research development if labels of convenience stating "Quebec-made" are issued or if vague or lax criteria allow for drugs that are not Quebec-based to be defined as such. However, it will be necessary to fine-tune a definition that doesn't exclude non-Quebec companies: while one of the objectives is to help Quebec companies, another is to encourage foreign companies to invest more and become firmly established here in Quebec.

Creating a biopharmaceutical company observatory to identify and be able to track their development would be needed.

02 Eliminating Silos

This kind of observatory's role is not only to create a directory of innovations that could be eligible for a specific form of support; it will also serve as a tool to **monitor an innovation's progress to accompany it throughout the development process and be able, at each stage of this development, to provide the appropriate forms of support.**

The main obstacle to this continuous support is the specific nature of innovations designed for human health. Throughout the process, biopharmaceutical companies will gradually shift their government partners. Initially, they will often be supported by the ministry of higher education (if their innovation originated in a university setting), then by agencies or ministries tied to the economy, such as the Ministry of Economy and Innovation or Investissement Québec, which are intent on optimizing the Québec Life Sciences Strategy. Later in their development, whether at the preclinical and clinical research or marketing stages, they will primarily deal with the health and social services network, the Ministry of Health and Social Services (MHSS), the *Centres intégrés universitaires de santé et de services sociaux* / CIUSSS - integrated university health and social services centres), the *Régie de l'assurance maladie du Québec* (RAMQ), or the INESSS.

But in Quebec, the transition from one world to the other is not a smooth and simple relay race. There is a disconnect between the worlds of economic development and healthcare, undoubtedly due to fears that collaboration will result in healthcare objectives (which are defined as a right) being corrupted by financial and commercial considerations.

This fear leads economic development policymakers to avoid venturing into a world where they are not welcome, while healthcare network officials don't even consider economic factors in their strategies. These mindsets are no doubt reinforced by the administrators of an essentially public network's lack of understanding and distrust of the pharmaceutical industry's more private nature and commercial approach to its operations. Essentially, the left hand doesn't know what the right hand is doing within this government system.

This disconnect interferes with the support given to innovations by interrupting its continuity. Solving this problem can be done by eliminating the silos that hinder the continuity and implementing communication and information-sharing mechanisms between economic and healthcare network agencies. The goal is to ensure that support available for a molecule or a drug's development does not encounter indifference, red tape, or bureaucratic inflexibility within the healthcare network.

03 Creating a Proactive Procurement Policy

Public procurement policies do not apply to a significant portion of the products that will result from biopharmaceutical innovations, as these are drugs that will be subject to INESSS' approval and reimbursed by the RAMQ, used in hospital settings following a recommendation notice by the INESSS, or part of an exception process.

However, certain biopharmaceutical products are not drugs that will be listed in Canada's Register of Innovative Drugs (such as vaccines and diagnostic tests) and may be subject to hospitals' purchasing policies or those of the MHSS, *Centres intégrés de santé et services sociaux*, and CIUSSS. This issue is more relevant to non-pharmaceutical biotechnology innovations, which are not covered in this report, even though some of this sector's companies are members of BIOQuébec. The same applies to medical technologies, which are not included in BIOQuébec's scope of activity.

The Quebec government is well aware of the power of purchasing policies. Its economic strategy asserts that as the largest purchaser of products and services in Quebec, the State plays a crucial role. The government can set the example by using this major economic lever to prioritize Quebec companies and products while staying within the parameters established by the applicable public procurement liberalization agreements.

In February 2022, the Quebec government released a new government procurement strategy that seeks, among other things, to make public procurement contracts more accessible to Quebec companies and use them to foster innovation.

While the purchasing policies issue is not central to biopharmaceutical innovations, it should be addressed quickly because how purchasing policies are formulated reflects the healthcare network's practices and attitudes and impacts the biopharmaceutical sector.

04 Valuing Innovation

The pandemic created several examples of the healthcare system neglecting Quebec-based products, indicating either a lack of natural reflex to support Quebec-based innovations or a degree of reluctance to welcome innovations. It also highlighted severe technological inadequacies, such as the use of fax machines or the limitations of various computer tools that would be inconceivable in other fields of activity. While anecdotal, these are disturbing indications that point to a resistance to innovation and difficulty adapting to change.

This underscores the fact that efforts to support Quebec-based innovations are unlikely to be successful if we do not manage to **counter the resistance to innovation within the network and establish a culture of change.**

The MHSS has focused on this issue by creating an important tool to transform its culture: the *Bureau de l'innovation en santé et en services sociaux*, a health and social services innovation office. Its mandate is to consult with the network's stakeholders to establish a priority list of the types of innovation to be integrated, work with life sciences members to meet those needs, and create productive partnerships between the health and social services network and industrial partners. It is also tasked with coordinating efforts to expedite the implementation of relevant and efficient innovations and contribute to Quebec's growth and competitiveness in the life sciences by stimulating the export potential of innovative companies that have proven themselves in the Quebec network. **This office could also assist in creating the synergies with economic development organizations suggested above.**

But the effort to support the use of Quebec-based products will not be successful in an acceptable timeframe without **very clear instructions from the Minister of Health and Social Services to the Ministry, and from the Ministry of Health and Social Services to its various departments, to prioritize these practices**.

05 Creating a Technology Showcase

In more innovation-focused sectors, another valuable tool for governments is **technology showcases**, which are used to feature local innovations to demonstrate know-how, as a calling card, to act as a lever to support other initiatives, or as an enticement to attract international partners. The use of technology showcases is understandably difficult to support if Quebec-based innovations are given worse consideration in Quebec than in Canada's other provinces. Molecules that have been denied market access obviously cannot be showcased. **This approach would allow Quebec-based biopharmaceutical innovations to be showcased and would be even more successful since it would support the innovation process in its entirety.**

For example, the healthcare network could support companies and research centres by providing a test environment for their innovations. This would be a way to foster clinical trials that would not require significant financial resources.

The Australian model is a good example: facilitate clinical studies and financially support clinical studies and biomanufacturing (of local companies or foreign companies associated with a local one). In other words, provide non-competitive advantages (as per international laws) to enhance the ecosystem's ability to host clinical demonstrations. Such an initiative could promote Quebec-based innovations and improve research centres' positioning.

06 Expanding the INESSS' Criteria

Preferential treatment could come from greater flexibility in the INESSS' recommendations for Quebec-based drugs. The agency does not consider the geographical origin of a drug or the country in which the company making the request is located. Currently, the origin of a drug is not a factor the INESSS takes into account in its analyses. **BIOQuébec believes that the Quebec-based nature of a drug should be taken into consideration.**

This is obviously not to suggest that such a product should benefit from a more accommodating assessment of its therapeutic value, but to introduce the idea that the Quebec-based origin of a drug has a positive effect on the innovation and healthcare systems and **can therefore constitute a positive element that must be considered as part of the added value**. For example, when the INESSS' workload leads to delays and backlogs, the INESSS could have the administrative directive to prioritize Quebec-based innovations.

In addition to the more traditional criteria of therapeutic value and efficiency, the INESSS also considers the public health consequences of a drug being on the Register and on the health and social services systems' other components.

These criteria, which have a very general scope, could certainly be mentioned when considering the fact that developing a drug in Quebec, by supporting the Quebec innovation ecosystem and stimulating research, strengthens the Quebec healthcare system, contributes to economic growth, and positively affects the healthcare system's other components.

This is why a **drug's origin should be included in the assessment criteria used by the INESSS** and become one of the factors used to establish its fair price.

07 Granting Price Advantages

While the INESSS considers the price of the drug as part of its assessment when establishing the relationship between the cost of a drug and its effectiveness, the actual price paid will be the result of negotiations between the company marketing the drug and an interprovincial agency, the pan-Canadian Pharmaceutical Alliance, which Quebec has joined, and which represents all the provinces. At the end of those negotiations, the Minister will decide whether or not to list the drug.

At this stage, the Minister could consider granting a price advantage - accepting to pay a price level that would be viewed as too high for a drug with a different origin – based on the argument that, from a cost-benefit perspective and bearing in mind public finances and the optimization of healthcare expenditures, **a drug developed in Quebec has a positive economic impact that must be considered.**

Including the drug origin factor of the origin of the drug in the price negotiation process between manufacturers and the public payer is all the easier to implement since negotiations with companies, like the prices paid, are confidential.

Quebec could also choose, in the case of Quebec-based drugs, to negotiate directly with the manufacturers rather than using the pan-Canadian Pharmaceutical Alliance's negotiation mechanism, since there is no binding aspect to this alliance.

However, consideration will need to be given to how this additional cost will be absorbed, either by the healthcare system, which would affect the resources available for other obligations, or by entities that manage financial resources allocated for economic development. Consideration could also be given to the development of cross-subsidization mechanisms designed to ensure that the additional costs of reimbursing a Quebec-based drug and which are intended for economic development purposes, are financed by economic mission budgets and do not affect healthcare budgets.

08 Introducing an Alert Mechanism

Support for Quebec-based innovations will also have to be centred on a clear desire from both the government and the Minister of Health. To ensure that this desire is reflected throughout the network and circumvents systemic resistance, ad hoc or discretionary measures may sometimes be appropriate, such as:

- **Ad hoc involvement by the Minister** to expedite the issuance of notices or approve a drug despite a rejection notice, on the basis of economic contribution considerations.
- **Standardizing the practice, which is accepted but rarely used, that allows the Minister to override a rejection notice from the INESSS when it involves a Quebec-based drug, except, of course, when the rejection is based on medical considerations.** Ideally, this practice should be formalized and controlled to avoid political arbitrariness.
- **Creating an alert mechanism to identify delays, bureaucratic red tape, anomalies, or injustices that could penalize a Quebec-based drug or innovation,** thus allowing for prompt action to be taken to correct the situation.

09 Supporting Research Through Access to Data

With its biological, clinical, and administrative data banks, Quebec has valuable tools to support biopharmaceutical research and innovation. These banks are rich in relevant information and are all the more comprehensive because Quebec's healthcare system is public, centralized, and complemented by a drug insurance plan which is unique in North America.

Having access to this data can be a powerful lever to position Quebec as a key stakeholder in the life sciences, yet the use of this comparative advantage meets with some resistance, which affects its acceptance by society. This is due in part to legitimate privacy concerns that must be addressed by implementing stringent security rules. But these concerns are also based on less rational elements and misinformation with which the government must contend.

These concerns caused the government to seek to restrict the use of this data to university research. Such an approach would significantly limit the optimal use of this information and prevent research and innovation from reaching their full potential.

University research plays an important role in Quebec, but research does not only occur in university settings. Even in the case of university-based innovations, a very large percentage of the research and development subsequently gets done in the private sector. A number of companies in Quebec also carry out very high-quality research. They are innovating and they also need access to data.

To support research and the development of life sciences, Quebecers should be able to benefit from their data, which should be accessible for research and the development of biopharmaceutical innovations.

This access must be strictly regulated, knowing that there is no such thing as zero risk (not in the biopharmaceutical field, nor in other spheres of human activity), and knowing that such access must be coupled with transparency measures and efforts to improve society's acceptance.

It should be acknowledged that in Quebec and in Canada's other provinces, this resistance from public authorities and the general public is due in large part to a degree of difficulty in accepting the coexistence of private activities within the mostly public healthcare field. These more social issues are the ones this report will briefly address in its conclusion, which can be found in the following section.

CONCLUSION: REDUCE INSTITUTIONAL CONSTRAINTS

However, implementing such policies will be difficult unless the constraints that currently delay the ability to meet the Quebec Life Sciences Strategy's objectives or impede the acceptance of Quebec-based drugs or innovations are lifted. It will undoubtedly be necessary to explore the nature of these constraints and participate in the public debate to lessen this resistance and formulate public policy ideas serving to develop public policy options.

In Quebec and across Canada, the reluctance to link the noble issue of healthcare to economic imperatives leads to a barrier between development policies and healthcare policies. This reluctance is mainly due to the deep attachment to our healthcare system's public nature, which

the other Canadian provinces view as part of their identity in relation to their American counterparts, and which Quebec considers an essential component of its solidarity. As such, this is a highly sensitive debate that inevitably revolves, in Quebec and in Canada's other provinces, around the opposition between public and private healthcare. It requires an approach that considers the experiences of European countries that are committed to social justice and have a less rigid view of what a public healthcare system should be, because they see the State's role as less of a service provider and more of a safeguard that ensures the quality and equity of these services.

By extension, this may explain a second issue: the strained relationship between the healthcare industry, which is essentially public, and the biopharmaceutical sector (and, more generally, the drug ecosystem, i.e., pharmaceuticals, pharmacies, insurers), which is essentially private. The healthcare system's management by medical authorities focuses on the elements covered by the public plan, particularly hospital and medical services. As a result, components outside this perimeter tend to be perceived as foreign bodies and are poorly integrated into planning and decision-making processes. Although the public plan partially covers drugs, the largely private drug industry as a whole suffers from this dichotomy.

Another barrier is a sense of mistrust towards drugs, medical products, and technologies, which the healthcare system perceives as costs and expenses rather than services. Moreover, drugs are mistakenly seen as a major reason for the steep increase in the cost of healthcare. **Therefore, actions must be taken to dispel these perceptions and show how drugs make a significant contribution to improving the healthcare system.**

Finally, we must deal with the health and social services network's remarkable rigidity and resistance to innovation, clearly evident during the COVID crisis. This resistance to, and fear of, change needs to be documented so that solutions can be put forward.

While not central to this project's approach, all these considerations could be included in the research project's second phase and contribute to meeting the primary goal of fully developing biopharmaceutical research.