Building on the Legacy of Vaccines in Canada: Value, Opportunities, and Challenges

7

Pathway to Access: Manufacturing, Supply, and Procurement Systems

BIOTECanada
Vaccine Industry Committee

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Series prepared on behalf of the Vaccine Industry Committee by: Nora Cutcliffe , PhD

BIOTECanada
130 Albert Street #420
Ottawa, ON K1P 5G4
613-230-5585
www.biotech.ca

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La voie de l'accès : Systèmes de fabrication et d'approvisionnement

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7.1.1 Executive Summary

Earlier papers in BIOTECanada's Vaccine Industry Committee (VIC) white paper series have underscored the tremendous value of vaccines, current marketplace dynamics and promising research opportunities, as well as the challenging regulatory, recommendation and funding environment within which vaccines are brought to market in Canada. This paper focuses on subsequent steps along the pathway to market access, including large-scale production and vaccine procurement systems – as critical elements in ensuring adequate vaccine supply and timely delivery to end-users. Securing access to a stable supply of recommended vaccines plays a fundamental role in assuring high levels of vaccination coverage for children, adolescents and adults, both in Canada and abroad. Clearly, since global demand for vaccines continues to outstrip supply, the security of vaccine supply remains a critical issue for all jurisdictions.

Today's vaccine manufacturing environment can be characterized as complex, costly, and highly regulated, particularly given the inherently variable nature of vaccines as biological entities. The production of a single lot of vaccine can take one to two years, with significant time (up to 70%) spent on quality and manufacturing controls to ensure the highest vaccine safety standards. In addition, building a new facility to increase production capacity also results in long lead times of three to five years, and may cost in the range of $US 100-600 million. Overall, long production lead times represent a fundamental challenge (and substantial risk) in vaccine manufacturing, and weigh heavily on production plans and facility investment decisions well in advance of regulatory approval. The recent outbreak of novel influenza A (H1N1) – first identified in April 2009, and declared as a Phase 6 pandemic alert by the World Health Organization (WHO) on June 11, 2009 – provides a timely example that highlights the difficulties of dealing with capacity constraints and compressed lead times for a rapid response and large-scale vaccine production.

In general, balancing vaccine supply and demand is viewed as a delicate, difficult task; uncertainties in the timing and magnitude of both supply-side constraints and demand-side drivers represent significant challenges for manufacturers in producing adequate vaccine supply. Taking this perspective, and in response to persisting concerns regarding the fragility of the domestic and international vaccine supply, a variety of proposals have been put forward to minimize future shortages. These strategies include both "push" and "pull" mechanisms (see Paper 3) to encourage continued investment in vaccine research and development (R&D), and to help ensure continued vaccine supply. Other proposals to strengthen the vaccine supply include subsidizing idle manufacturing capacity that could be used in emergencies, use of foreign suppliers during temporary shortages, and use of more accurate forecasting methods to predict vaccine demand. Active implementation of such proposals should facilitate "connecting the dots" in achieving crystal-clear recognition that a secure vaccine supply plays a vital role in the delivery of predictable immunization programs – to help meet a range of fundamental public health objectives.

In the context of vaccine supply issues, critical attention must also be paid to cold chain management (to keep vaccines within an appropriate temperature range) throughout the distribution and storage process. In particular, temperature fluctuations or extremes may negatively affect vaccine stability, potency, safety or efficacy, and may also contribute to waste – because compromised vaccines may need to be destroyed. Notably, the VIC has recently proposed to work in partnership with the provinces/territories and Health Canada to provide available vaccine stability data to vaccine users, i.e. while continuing to use the vaccine product monograph as the principal guidance document for stability information.

In Canada, procurement procedures for purchasing vaccines are complex and cumbersome. Essentially, after overcoming significant R&D, regulatory, recommendation and financing challenges (refer to Papers 3, 4, 5 and 6), manufacturers must also engage in competitive contract negotiations as one of the final major steps prior to delivering vaccines to Canadians. Within the current federal/provincial/territorial (F/P/T) bulk purchasing program, Public Works and Government Services Canada (PWGSC) acts as an agent of the Vaccine Supply Working Group (VSWG) to manage vaccine tenders/contracts on behalf of all jurisdictions. The tender process is often based on a "winner take all" strategy, in which all sales for a given vaccine are awarded to the lowest price bidder. More recently, in efforts to promote security of the vaccine supply, there has been a trend towards dual-supplier contracts, in which up to two suppliers provide the required vaccine doses for all regions. Such dual awards can only be implemented when advisory committees consider competitor vaccines similar enough to be fully "interchangeable". Apart from the (public) F/P/T bulk purchasing program, other procurement systems in Canada include direct contracts between individual jurisdictions and vaccine suppliers, and private sector mechanisms.

Canada's vaccine procurement environment has several limitations which are cause for concern among vaccine manufacturers. First, the current vaccine procurement framework tends to treat vaccines as low-tech commodities; it does not adequately recognize vaccines as high-value biotechnology products, with proven value in disease prevention. Second, within the public sector, the government acts as a single powerful buyer with significant bulk purchasing power – placing downward pressure on price. This primary price focus has driven vaccine prices in Canada to among the lowest in the developed world, thus reducing industry profit margins, and discouraging potential new entrants into the Canadian vaccine market. In addition, the strong price emphasis fails to recognize other important social values, e.g. by limiting Canada's contribution to maintaining subsidized pricing structures for the world's poorest nations.

In addition, other parameters within the current procurement environment – specifically those pertaining to contractual design – can contribute directly to vaccine waste. These factors may include one or more of the following constraints: i) insufficient lead time for initial vaccine delivery, optional contract extensions, and optional quantities; ii) mandatory return policies; and iii) the lack of appropriate/unique cold chain clauses for individual vaccines. By encouraging vaccine waste, the current procurement system effectively increases production costs and decreases production capacity for manufacturers. More importantly, from a public health perspective, vaccine waste is associated with the opportunity cost of missed vaccination for individuals in other jurisdictions, who may go without the benefits of immunization. Moreover, since worldwide demand for vaccines exceeds supply, both government and industry players have a moral obligation to protect global vaccine supplies by minimizing waste.

Since vaccine procurement is a shared responsibility across manufacturers, federal government agencies and P/T public health authorities, all stakeholders should aim to work in partnership to improve current policies through appropriate procurement reform. Collectively, all partners in immunization must work towards enhancing the effectiveness and efficiency of vaccine procurement systems for the benefit of Canadians – by creating an environment conducive to meeting both industry and public health objectives in implementing vaccine program strategies. Continued progress towards a revitalized, fair procurement process will be required to help secure a more reliable, robust vaccine supply, and to achieve the common goal of providing timely patient access to high-value vaccines. In the spirit of such collaboration, the VIC has put forward the following recommendations for consideration by key F/P/T government stakeholders.

Federal/Provincial/Territorial (F/P/T) Recommendations

1. In view of long production lead times, and the complex, costly, and highly regulated nature of the vaccine manufacturing environment, policy approaches to developing an efficient vaccine marketplace should encourage long-term investment in Canadian-based innovation, R&D and manufacturing capacity within the vaccine sector. Such initiatives, including both "push" and "pull" strategies, should assist in preventing manufacturers from exiting the vaccine market, and ensuring continued supply of existing and emerging high-value vaccines (see also Paper 3).

2. Regarding vaccine pricing, increased recognition is required by designated users regarding the true value of the vaccine supply chain – and that lowest price does not necessarily deliver greatest value.

    - Implementation of more favourable pricing structures for vaccines (including appropriate tender-based evaluation criteria) could stimulate the economy by encouraging R&D to create innovative vaccine products, while fostering future job creation and a more robust tax revenue base.
    - Pricing barriers that stand in the way of competitive market profitability – including strict regulation of patented vaccines by the Patented Medicine Prices Review Board (PMPRB) – should be removed, or undergo reform, to help strengthen the vaccine enterprise, i.e. by encouraging companies to continue to risk investment capital to build future production capacity.

3. In working towards an optimal, modern, fair and transparent vaccine procurement system, the following revisions should be made to specific terms/conditions in improving current PWGSC/VSWG contract design (and ideally also for direct contracts with individual jurisdictions, where appropriate).

    - With regard to contractual obligations (e.g. mandatory requirements): i) Users should allow sufficient lead time (six months minimum) for initial delivery, contract extensions, and volume increases for optional quantities, i.e. to ensure manufacturers can adjust supplies to meet global demand; and ii) Users should be required to pay for minimum quantities, regardless of usage, i.e. to encourage better program planning and more accurate demand forecasting.
    - With respect to minimum return policies, the VSWG should work in close cooperation with the VIC to reduce the need for vaccine returns, i.e. by developing methods to ensure that vaccine quantities ordered are indeed utilized.
    - Regarding cold chain supply management, policies and procedures should also be put in place to educate and monitor relevant stakeholders/users regarding storage and handling requirements, with the goal of mitigating losses due to vaccine waste.
    - In the event of inability to supply vaccine, the contract should limit financial liability to the amount specified in the contract during the period of inability to supply, and the manufacturer should be allowed to terminate a contract with six months notice (for a long-term interruption).

4. To ensure the effectiveness, efficiency, value and success of Canada's publicly-funded immunization programs, continued efforts are required to further improve and enhance Canada's vaccine procurement system by building collaborative partnerships across key stakeholders (including manufacturers, federal government agencies, P/T public health authorities, and academia).

    - The VIC has proposed to establish a dedicated working group – with representatives from the Public Health Agency of Canada (PHAC), the VSWG, provinces/territories, the Biologics and Genetic Therapies Directorate (BGTD), and industry – to address supply chain management issues, with particular emphasis on strengthening terms and conditions pertaining to vaccine forecasting and procurement lead times, cold chain requirements and product stability guidelines.

5. Continued efforts should be made by F/P/T policy makers to explore and consider alternative vaccine procurement systems currently in place in other developed countries, i.e. to identify key lessons and best practices that merit consideration in the context of the current Canadian vaccine landscape.

7.1.2 Sommaire

Des documents du Comité de l'industrie des vaccins (CIV) de BIOTECanada publiés précédemment dans le cadre d'une série de dix soulignent la valeur importante des vaccins, la dynamique actuelle des marchés et les débouchés prometteurs dans le secteur de la recherche, de même que les défis auxquels se frotte la commercialisation des vaccins au Canada sur le plan de la réglementation, des recommandations et du financement. Le présent document traite des étapes subséquentes du processus d'accès aux marchés, y compris les systèmes de production à grande échelle et d'approvisionnement des vaccins, éléments essentiels de l'approvisionnement de vaccins en quantités suffisantes et de leur administration aux utilisateurs finals en temps opportun. Afin d'assurer une couverture vaccinale élevée chez les enfants, les adolescents et les adultes, tant au Canada qu'à l'étranger, il est fondamental d'avoir accès à un approvisionnement stable des vaccins recommandés. Étant donné que la demande mondiale en matière de vaccins continue de dépasser l'offre, il est évident que la sécurité de l'approvisionnement en vaccins demeure un enjeu important pour tous les pays.

Le contexte actuel de la fabrication des vaccins peut être qualifié de complexe, coûteux et hautement réglementé, compte tenu notamment du caractère intrinsèquement variable des entités biologiques que sont les vaccins. La production d'un seul lot de vaccins peut s'échelonner sur une période de deux ans, dont une partie importante (jusqu'à 70 %) est consacrée aux systèmes de contrôle de la qualité et de la production afin de respecter les normes les plus élevées d'innocuité des vaccins. La construction de nouvelles installations visant à accroître la capacité de production occasionne également des délais d'approvisionnement de trois à cinq ans et peut générer des coûts variant de 100 à 600 millions de dollars américains. En général, les délais de production élevés constituent un défi de taille pour la fabrication des vaccins (en plus de présenter des risques importants) et pèsent beaucoup dans les plans de production et les décisions d'investir dans de nouvelles installations, bien avant l'approbation réglementaire. L'éclosion récente de la grippe A (H1N1) – dont les premiers cas ont été signalés en avril 2009 et dont la propagation a forcé l'Organisation mondiale de la Santé (OMS) à hausser son alerte au niveau 6 le 11 juin suivant – démontre combien il est difficile de gérer les contraintes de capacité et les délais de production serrés quand il s'agit de réagir rapidement et de produire des vaccins à grande échelle.

En matière de vaccins, établir un équilibre entre l'offre et la demande est considéré, en général, comme une tâche délicate et difficile; les incertitudes que suscitent l'ampleur des contraintes liées à l'offre et des incitatifs liés à la demande, et le moment de leur apparition représentent un défi de taille pour les fabricants qui souhaitent produire des vaccins en quantités suffisantes. Considérant ce point de vue et en réponse aux préoccupations incessantes concernant la fragilité de l'approvisionnement national et international en vaccins, on a présenté divers projets visant à minimiser les pénuries futures, dont des stratégies « de pression » et « d'attraction » (voir le document 3), destinées à encourager l'investissement continu dans la recherche et le développement (R et D) de vaccins, et à assurer un approvisionnement constant en vaccins. D'autres projets visant à renforcer l'approvisionnement en vaccins consistent à subventionner la capacité de production inutilisée pouvant servir aux situations d'urgence, à recourir à des fournisseurs étrangers durant les pénuries temporaires et à employer des méthodes plus précises pour prédire la demande en vaccins. La mise en œuvre active de ces projets devrait contribuer à « rassembler les pièces du casse-tête » pour admettre clairement que la sécurité de l'approvisionnement en vaccins est essentielle à la prestation de programmes d'immunisation prévisibles – afin de répondre à un éventail d'objectifs fondamentaux en matière de santé publique.

Au chapitre des enjeux liés à l'approvisionnement en vaccins, une attention particulière doit aussi être portée à la gestion de la chaîne du froid (afin de conserver les vaccins à des températures adéquates) durant tout le processus de distribution et d'entreposage. Les fluctuations ou extrêmes de température, notamment, peuvent nuire à la stabilité, à la puissance, à l'innocuité ou à l'efficacité des vaccins et contribuer au gaspillage dû à la destruction possible des vaccins affaiblis. Le CIV a notamment proposé récemment de travailler en collaboration avec les provinces et territoires, de même qu'avec Santé Canada, afin de fournir aux utilisateurs de vaccins des données disponibles sur la stabilité des vaccins, tout en leur recommandant, par exemple, de continuer d'utiliser la monographie du vaccin comme principal document d'orientation pour obtenir des renseignements sur la stabilité du produit.

Au Canada, l'achat de vaccins est un processus complexe et laborieux. Fondamentalement, après avoir surmonté des défis importants sur le plan de la R et D, de la réglementation, des recommandations et du financement (voir les documents 3, 4, 5 et 6), les fabricants doivent également se livrer à des négociations de contrats serrées, l'une des dernières étapes importantes de l'approvisionnement des Canadiens en vaccins. Dans le cadre du programme fédéral-provincial-territorial (FPT) d'achat en vrac actuellement en place, Travaux publics et Services gouvernementaux Canada (TPSGC) fait office d'agent du Groupe de travail sur l'approvisionnement en vaccins (GTAV), chargé de gérer, au nom de tous les gouvernements, les soumissions et contrats en matière de vaccins. Le processus d'appel d'offres s'appuie souvent sur le principe du « tout au vainqueur », selon lequel le soumissionnaire offrant le prix le plus bas obtient la vente exclusive d'un produit donné. Dans un effort visant à promouvoir la sécurité de l'approvisionnement en vaccins, on a observé, tout récemment, une tendance favorisant l'adjudication de contrats à deux entreprises, dans le cadre desquels elles doivent produire les doses vaccinales requises pour toutes les régions. Ce double octroi ne peut avoir lieu que lorsque des comités consultatifs jugent que des vaccins concurrents sont assez semblables pour être pleinement « interchangeables ». Outre le programme FPT d'achat en vrac, le Canada compte d'autres systèmes d'approvisionnement, dont des contrats directs entre fournisseurs et gouvernements, et des ententes avec le secteur privé.

Le système canadien d'approvisionnement en vaccins comporte diverses restrictions, qui suscitent des préoccupations chez les fabricants de vaccins. D'abord, on a tendance à y considérer les vaccins comme des produits à faible technologie et non, comme il se doit, des produits biotechnologiques de grande valeur, ayant fait leurs preuves en matière de prévention des maladies. Ensuite, au sein du secteur public, le gouvernement fait fonction d'acheteur puissant qui, doté d'un pouvoir d'achat en vrac considérable, exerce une pression à la baisse sur le prix. Cette attention importante dirigée vers le prix fait en sorte que le prix des vaccins au Canada se situe parmi les plus bas au sein des pays développés, ce qui réduit la marge de profit de l'industrie et nuit à l'entrée possible de nouveaux acteurs sur le marché canadien des vaccins. En insistant fortement sur une baisse des prix, le gouvernement néglige également d'autres valeurs sociales importantes, limitant, par exemple, la contribution du Canada au maintien de tarifications subventionnées pour les pays les plus pauvres du monde.

D'autres éléments du système actuel d'approvisionnement – liés notamment à la nature des contrats – peuvent aussi contribuer directement au gaspillage des vaccins. Parmi ceux-ci, on compte l'une ou plusieurs des contraintes suivantes : i) temps insuffisant pour la production initiale des vaccins, les prolongations facultatives de contrat et les hausses du volume des quantités optionnelles; ii) politiques de retour obligatoire; iii) absence de clauses adéquates et uniques visant chaque vaccin relativement à la chaîne de froid. En encourageant le gaspillage, le système actuel d'approvisionnement accroît les coûts de production de manière frappante et diminue la capacité de production des fabricants. Du point de vue de la santé publique, le gaspillage est surtout associé au coût des occasions ratées de vaccination chez des personnes d'autres pays, qui peuvent ne jamais connaître les avantages de l'immunisation. En outre, comme la demande mondiale en vaccins excède l'offre, le gouvernement et l'industrie ont tous deux l'obligation morale de protéger les réserves mondiales en minimisant le gaspillage.

Étant donné que l'approvisionnement en vaccins est une responsabilité que doivent se partager les fabricants, les organismes fédéraux et les autorités provinciales et territoriales en matière de santé publique, tous les intervenants doivent s'efforcer de travailler ensemble afin d'améliorer les politiques actuelles dans le cadre d'une réforme adéquate du système d'approvisionnement. Ensemble, tous les intervenants en matière d'immunisation doivent travailler à améliorer l'efficacité des systèmes d'approvisionnement en vaccins au profit des Canadiens en créant un environnement favorable à la réalisation des objectifs de l'industrie et du secteur de la santé publique liés à la mise en œuvre de programmes de vaccination. Des progrès continus en vue de créer un système d'approvisionnement équitable, insufflé d'un dynamisme nouveau, devront être accomplis pour que l'approvisionnement en vaccins soit plus fiable et plus rigoureux, et pour que soit réalisé l'objectif commun visant à améliorer l'accès des patients à des vaccins de grande valeur. Dans cet esprit de collaboration, le CIV a formulé les recommandations suivantes à l'intention des gouvernements fédéraux, provinciaux et territoriaux.

Recommandations à l'intention des gouvernements fédéraux, provinciaux et territoriaux

1. Concernant la lenteur des délais de production et l'environnement complexe, coûteux et hautement réglementé de la fabrication des vaccins, les approches politiques à l'égard du développement d'un marché efficace doivent favoriser l'investissement à long terme dans l'innovation, la R et D et la capacité de fabrication au sein du secteur des vaccins au Canada. Ces approches, y compris les stratégies « de pression » et « d'attraction », doivent contribuer à empêcher les fabricants de sortir du marché et à assurer un approvisionnement continu en vaccins de grande valeur, tant actuels que nouveaux (voir le document 3).

2. Concernant le prix des vaccins, les utilisateurs déterminés doivent mieux reconnaître la vraie valeur de la chaîne d'approvisionnement des vaccins – et être mieux sensibilisés au fait que le prix le plus bas n'est pas nécessairement gage d'une valeur optimale.

    - L'application de structures plus favorables de fixation des prix des vaccins (y compris des critères adéquats d'évaluation des soumissions) pourrait stimuler l'économie, car elle encouragerait les chercheurs à créer des produits innovateurs, tout en favorisant la création d'emplois futurs et garantissant une assiette fiscale plus solide.
    - Les structures de prix qui font entrave à la rentabilité concurrentielle du marché, y compris la réglementation rigoureuse établie par le Conseil d'examen du prix des médicaments brevetés (CEPMB) à l'égard des vaccins brevetés, doivent être supprimées ou réformées afin de renforcer le secteur des vaccins, notamment en incitant les compagnies à continuer d'investir des capitaux dans le renforcement de leur capacité de production.

3. Afin de créer un système d'approvisionnement en vaccins qui soit optimal, moderne, équitable et transparent, il conviendrait d'apporter les améliorations suivantes aux conditions particulières de l'entente de TPSGC et du GTAV (et, idéalement, aux contrats directs établis avec chaque gouvernement, au besoin).

    - En ce qui concerne les obligations contractuelles (p. ex., les exigences obligatoires) : i) Les utilisateurs devraient prévoir suffisamment de temps (au moins six mois) pour la production initiale, les prolongations de contrat et les hausses du volume des quantités optionnelles, pour faire en sorte, notamment, que les fabricants puissent accroître leur approvisionnement en fonction de la demande mondiale; ii) Les utilisateurs devraient être tenus de payer des quantités minimales, sans égard à l'usage, au profit, notamment, d'une planification plus efficace des programmes et d'une prévision plus juste de la demande.
    - Concernant les politiques minimales de retour, le GTAV doit travailler en étroite collaboration avec le CIV afin de réduire la nécessité de retourner des vaccins, notamment en élaborant des méthodes permettant de vérifier si les quantités de vaccins commandées sont bel et bien utilisées.
    - Quant à la gestion de la chaîne de froid, on doit mettre en place des politiques et des procédures visant à informer les intervenants et utilisateurs concernés au sujet des exigences relatives à l'entreposage et à la manutention, et en surveiller la conformité, afin de réduire les pertes dues au gaspillage.
    - Si le fabricant est incapable de fournir le vaccin, le contrat doit limiter sa responsabilité financière au montant qui y est énoncé pendant la période d'incapacité, et l'on doit lui permettre de mettre fin au contrat en donnant un avis de six mois (dans le cas d'une interruption à long terme).

4. Afin de promouvoir la valeur des programmes publics d'immunisation au Canada, et d'en assurer l'efficacité et le succès, on doit poursuivre les efforts visant à améliorer davantage le système canadien d'approvisionnement en vaccins en établissant des partenariats de collaboration entre principaux intervenants (y compris les fabricants, les organismes fédéraux, les autorités provinciales et territoriales en matière de santé publique, et le milieu universitaire).

- Le CIV a proposé de constituer un groupe de travail (composé de représentants de l'Agence de la santé publique du Canada (ASPC), du GTAV, des provinces et territoires, de la Direction des produits biologiques et des thérapies génétiques (DPBTG) et de l'industrie), chargé de gérer les questions liées à la gestion de la chaîne de froid, en insistant particulièrement sur le renforcement des conditions relatives aux délais de prévision de la demande en vaccins et d'approvisionnement, aux exigences concernant la chaîne de froid et aux lignes directrices relatives à la stabilité des produits.

5. Les décideurs fédéraux, provinciaux et territoriaux doivent poursuivre leurs efforts en vue d'étudier et d'examiner les systèmes d'approvisionnement actuellement en place dans d'autres pays développés, afin notamment d'en tirer des leçons importantes et de déterminer les pratiques exemplaires qui méritent d'être examinées dans le cadre de l'environnement actuel des vaccins au Canada.

7.2 Vaccine Manufacturing Environment

Earlier papers in BIOTECanada's Vaccine Industry Committee (VIC) white paper series have underscored the tremendous value of vaccines, current marketplace dynamics and promising research opportunities, as well as the challenging regulatory, recommendation and funding environment within which vaccines are brought to market in Canada. In turn, this paper focuses on subsequent steps along the pathway to market access in Canada, i.e. large-scale production, vaccine procurement and distribution – as critical elements in ensuring adequate vaccine supply and timely delivery to end-users. Securing access to a stable supply of recommended vaccines plays a fundamental role in assuring high levels of vaccination coverage for children, adolescents and adults, both in Canada and abroad. Clearly, since global demand for vaccines continues to outstrip supply, the security of vaccine supply remains a critical issue for all jurisdictions.[1]

In general, today's vaccine manufacturing environment can be characterized as complex and highly regulated, particularly given the inherently variable nature of vaccines as biological entities (see Paper 4). Globally, the vaccine industry has undergone significant consolidation; over the past 30 years, the number of companies engaged in large-scale vaccine production has declined from roughly 25 to five.[2] Key factors that have contributed to the decision for several companies to abandon vaccine production – and which also represent formidable challenges faced by potential new entrants – include strict regulatory oversight and increasing compliance requirements; the concomitant high cost of vaccine development, clinical research and specialized facilities; the imbalance between cost and pricing structures (resulting in narrow profit margins); difficulties in predicting demand, coupled with long production lead times; and potential threats of liability lawsuits, particularly in the United States.[3, 4, 5]

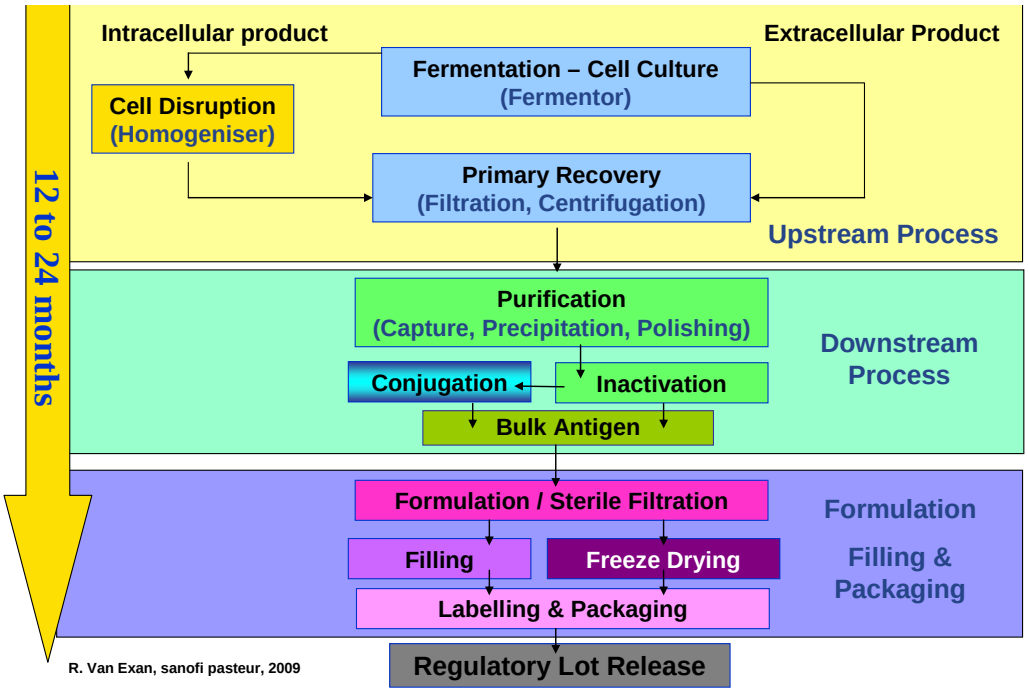
As many firms have exited the business (or have been acquired) over the past few decades, significant concern has been voiced regarding the fragility of the vaccine supply and the potential for future shortages of specific vaccines (as described in further detail in Section 7.5.2 below). However, it is generally believed that the few remaining players are better positioned as efficient manufacturers, and stand to gain from the renewed interest in the vaccine business (see Paper 3).[6] Indeed, recent growth in vaccine revenues (led by sales of "blockbuster" products such as Pfizer's Prevnar and Merck's Gardasil), combined with the future promise of new vaccine technologies and delivery methods, have helped to strengthen manufacturing infrastructure and international vaccine production capacity.[7]

Currently, the global vaccines market is dominated by the following "big pharma" players engaged in vaccine production: Merck & Co., sanofi-aventis, GlaxoSmithKline (GSK), Pfizer, and Novartis. Headquartered in Europe (sanofi-aventis, GSK, Novartis) and the United States (Merck, Pfizer), these multinational companies are responsible for roughly 90% of vaccine sales globally. Other smaller players among the top 10 global vaccine companies include Baxter International, Crucell, Solvay, Bavarian Nordic, and AstraZeneca.[8] In general, participation in the vaccine sector is limited to a small group of manufacturers capable of mobilizing the significant capital and highly skilled human resources necessary for vaccine development and commercial production.[9] In Canada, sanofi pasteur (the vaccine division of sanofi-aventis) has a large-scale vaccine manufacturing facility based in Toronto (known as the Connaught Campus),[10] and GSK has vaccine production facilities in Québec City and Laval, Québec.[11] Merck, Pfizer and Novartis do not presently have vaccine manufacturing facilities in Canada. Collectively, all five companies provide a broad range of vaccines that are currently approved for use in Canada (see Paper 2, Table 2.4).

7.3 General Vaccine Production Process

A wide range of technologies is used for vaccine manufacturing, including methods that employ killed, inactivated pathogens; live, attenuated agents; and purified protein, polysaccharide or deoxyribonucleic acid (DNA) components derived from viruses or bacteria (see Paper 1). While vaccine production processes are highly complex, lengthy and specialized to handle live pathogens – and precise methods can vary substantially for different vaccines – some generalizations can nevertheless be made (refer to Figure 7.1). All vaccine production involves the growth (fermentation) and harvesting of pathogens, usually involving the disease-causing microorganism, or another pathogen that has been modified or genetically altered to produce the antigenic characteristics of the disease-causing agent.[12]

Figure 7.1 – General Vaccine Production



In the "upstream" fermentation or cultivation stage, pathogenic organisms are grown under sterile manufacturing conditions, which require careful temperature control and specific types of growth media. For example, viruses need a cell substrate and hence can only be grown in living cells, such as cell cultures and fertilized hen's eggs. Following the growth phase, additional recovery and purification steps are taken to isolate the microorganism and remove impurities, e.g. via centrifugation, filtration or chromatography. In some cases, the pathogen is inactivated, whereas in other cases, the pathogen is broken down into component parts, and specific molecules with the appropriate antigenic characteristics are isolated to create the basis of the vaccine. During these "downstream" processes, the active component of the vaccine is isolated and combined with other materials to produce what is known as "bulk antigen". The bulk product is then formulated with appropriate stabilizers, preservatives, blending agents (e.g. additional pathogenic strains) or other antigens, i.e. for combination vaccines. Subsequently, the product is prepared for sterile filling into suitable containers (typically requiring high throughput of low volume ampoules), followed by visual inspection and labeling/packaging for shipment, according to market needs (see Section 7.5.4 regarding specific cold chain storage and handling requirements). The final filling and packaging process may involve freeze-drying to extend the product's shelf-life.

Throughout the production process, stringent quality control (QC) procedures are used to verify that the vaccine product contains the desired antigenic material and is free of potential contaminants. QC testing involves rigourous analysis and demonstration of desired specifications regarding product identity, characterization, quantity, purity, sterility, immunogenic activity and potency (in relevant animal models).[13] Additional QC tests are performed after final packaging to ensure that the packaging process has not altered the safety or potency of the vaccine product. Finally, samples from each batch are sent to Health Canada's Biologics and Genetic Therapies Directorate (BGTD) and potentially other regulators outside Canada for independent testing, lot release evaluation, and approval. Following vaccine approval, a lot release program ensures that new batches of the vaccine retain the same characteristics as those used to first establish quality, safety and efficacy. Furthermore, government programs administered through Health Canada continue to monitor vaccine effectiveness and safety on an ongoing basis (see Paper 4).[14]

The production of one lot of vaccine can take one to two years, with significant time (up to 70%) spent on QC and manufacturing controls to ensure the highest quality and safety standards.[15] In addition, building a new facility to increase production capacity also results in long lead times of three to five years,[16] and may cost in the range of $US 100-600 million.[17] Moreover, many different technologies exist for modern vaccine production, and unique facilities and/or dedicated equipment may be necessary for each vaccine (or category).[18] Thus, as aptly described by Alex Azar, Deputy Secretary, U.S. Department of Health and Human Services, vaccine production capabilities cannot be considered as "floodlights that can be switched on when you hear a noise outside".[19] Overall, long production lead times represent a fundamental challenge – and substantial risk – in vaccine manufacturing, and weigh heavily on production plans and facility investment decisions well in advance of regulatory approval. Future opportunities to reduce vaccine production timelines and costs, as reviewed elsewhere[20,21,22] include the use of: i) modern molecular techniques such as recombinant and plant-based technologies; ii) cell cultures to replace egg-based methods; iii) common platforms to produce more than one antigen; and iv) disposable bioreactors in place of fixed equipment.

7.4 Emerging Influenza A (H1N1) – Compressed Production Lead Times

The recent outbreak of novel influenza A (H1N1)[i] – first identified in April 2009, and declared as a Phase 6 pandemic alert by the World Health Organization (WHO)[23] on June 11, 2009 – provides an excellent example of the difficulties of dealing with potential manufacturing capacity constraints and compressed lead times for large-scale vaccine production. In Canada, GlaxoSmithKline (GSK) has a long-standing contract with the Canadian government to provide pandemic flu vaccine for all Canadians, yet there has been speculation that adequate quantities of H1N1 flu vaccine may not be available in time for the expected "second wave" of pandemic flu cases, anticipated for the early fall of 2009.[24] The pressure to expedite the manufacturing process for H1N1 flu vaccine has been extremely intense, particularly given that production, regulatory approval, and distribution of seasonal influenza vaccine (as the closest comparator) normally takes approximately eight months, beginning as soon as possible soon after February each year.[ii] Indeed, the pathway to market for seasonal influenza vaccine is already considered to be greatly accelerated, relative to most other vaccines.[25]

Very recently, vaccine makers currently developing vaccine candidates for the pandemic swine flu (using both egg-based and cell culture technologies) have advised the WHO that the influenza seed strain used to produce the new vaccine is not growing as well as expected, and is therefore giving poor antigen yields – approximately 25-50% of the yield vaccine manufacturers typically obtain for seasonal flu vaccine production.[26] This limitation has not yet been confirmed by GSK regarding yield at its Canadian facility. Interestingly, as of the end of July 2009, MedImmune,[iii] a U.S. based company that manufacturers an H1N1 nasal spray vaccine using a weakened live virus (rather than the inactivated H1N1 virus used by other manufacturers)[iv] has announced that its pace of production is faster than expected, providing a vaccine surplus. Hence, it has been suggested that the H1N1 nasal spray vaccine (known as FluMist) may gain accelerated approval in countries outside the U.S., particularly if anticipated shortages in the timely production of conventional pandemic flu vaccines are realized.[27] Overall, a long list of critical questions pertaining to H1N1 influenza vaccine currently remains unanswered – not only regarding the timing of vaccine availability for Canada and other countries – but also pertaining to vaccine safety, efficacy, packaging, delivery, and priority lists for immunization.[28,29]

7.5 Vaccine Supply Management

7.5.1 Balancing Vaccine Supply and Demand

The high fixed costs associated with manufacturing each lot of vaccine, combined with the inherently perishable nature of the finished (biologic) product, provide strong incentives for manufacturers to closely match production volume with anticipated demand. Vaccine manufacturers typically tend to be conservative in estimating vaccine demand – and thus in determining production capacity – in attempt to avoid holding large inventories that may remain unused.[30] Conversely however, from a public health standpoint, any shortage in vaccine supply increases the risks of both lower rates of vaccine coverage, and higher rates of vaccine-preventable disease.[31] Thus, matching supply with the (often unpredictable) demand for vaccines represents a delicate, difficult balancing act for myriad reasons, many of which are interrelated, and based on both known and unknown events (refer to Table 7.1). In general, uncertainties in the timing, magnitude, and impact of both supply-side constraints and demand-side drivers represent significant challenges for manufacturers in producing adequate vaccine supply. Inevitably, sporadic supply disruptions continue to occur for several existing vaccines, including those for influenza and meningococcus in Canada,[32] as well as for other vaccines in the U.S. and other countries.[33,34]

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i H1N1 refers to hemagglutinin sub-type 1, neuraminidase sub-type 1 (of the influenza A virus); H1N1 flu is referred to as the "swine flu".

ii In preparation for the annual "flu season" (anticipated to begin in October each year), three specific seasonal influenza strains are typically selected by the WHO in February, and viral strain seed stock is subsequently provided to influenza vaccine manufacturers worldwide to begin the annual vaccine production cycle.

iii MedImmune was acquired by AstraZeneca in 2007.

iv Both vaccine production methods (using live, attenuated or inactivated H1N1 virus) use chicken eggs for production.

Table 7.1 – Factors Affecting the Balance of Vaccine Supply and Demand [35,36,37]

Supply-Side Constraints	Demand-Side Drivers
• Few suppliers (industry consolidation), due to increasing cost, complexity, and regulatory oversight within current vaccine manufacturing environment (see Section 7.2) • Long production and capacity lead times (1-2 years per lot and 3-5 years for new facility) • Production constraints o Process changes (requirements to remove animal-based or blood products, or thimerosal) o Manufacturing problems (low yield, or potential lot failures due to increasingly stringent regulatory compliance requirements) • Recent trends toward "Just-In-Time" business practices, i.e. to reduce inventory and waste by delivering on as-needed basis (thus discouraging stockpiling) • Post-production challenges (see Table 7.3) o Vaccine wastage linked to procurement policy, including returns by potential users o Cold chain disruption	• General trend toward increased demand for existing and future vaccines (across childhood, adolescent and adult populations) • Emerging diseases, such as SARS, influenza A (H1N1) and other pre-pandemic influenza strains • Bioterrorist threats (anthrax, smallpox, Ebola) • Sporadic disease outbreaks (e.g. meningococcal outbreak in Canada, 1992-1993; mumps outbreak in Canada, 2007-2008) [38,39] • Public health policy environment (e.g. NACI/CIC recommendations; federal/provincial/territorial government funding) • Uptake and coverage rates for immunization programs in both the public and private sectors • Public awareness (e.g. significant increases in influenza awareness and coverage rates in Canada since late 1980s)[v]

SARS = severe acute respiratory syndrome (for which a vaccine is currently under development)

NACI = National Advisory Committee on Immunization

CIC = Canadian Immunization Committee

[v] Demand for influenza vaccines also rose sharply (by roughly 85%) between 1999 and 2000, when Ontario introduced its universal influenza immunization program; Source: Van Exan, R. Current Challenges In Immunization, The Delicate Balance of Vaccine Supply & Demand, Slide Presentation, Public Health WORKS Speaker Series, Sept. 20/05.

7.5.2 Preventing Vaccine Shortages

Overall, vaccine shortages can threaten the health of children and adults, cause significant disruption to the operations of health care providers, and undermine public confidence in the benefits of vaccines.[40] In response to serious concerns regarding the fragility of the domestic and international vaccine supply, a variety of proposals have been put forward to minimize future shortages. For example, as described in Paper 3, both "push" and "pull" strategies can be used to help develop an efficient vaccine marketplace – not only by encouraging investment in vaccine research and development (R&D) – but also by helping to ensure continued vaccine supply. While push mechanisms aim to reduce the cost burden of vaccine R&D (e.g. via government grants or tax incentives), pull strategies aim to increase demand volume or enhance product prices, including implementation of strategic procurement policies (see Section 7.6) and purchase guarantees (e.g. through Advanced Market Commitments). Pull strategies also include stockpiling in anticipation of periods when supply will be insufficient (e.g. for smallpox and pre-pandemic influenza vaccines).[41]

Other proposals to strengthen the vaccine supply include subsidizing idle capacity that could be used in emergencies, i.e. in the event of failure or force majeure (e.g. "act of God") disruption in active production of recommended vaccines,[42] and the use of foreign suppliers during temporary shortages – through accelerated domestic approval for vaccines licensed in other jurisdictions.[43] Finally, other more general approaches to help prevent vaccine shortages include streamlining and harmonizing regulatory practices, enhancing legal-liability protection, and use of more accurate demand forecasting methods.[44] Collectively, these strategies to promote a more reliable, robust vaccine supply should go a long way towards improving the ability of the vaccine enterprise to meet a range of critical public health objectives. Specifically, enhanced awareness and active implementation of such proposals should facilitate "connecting the dots" in achieving crystal-clear recognition that a secure vaccine supply plays a fundamental role in the delivery of predictable immunization programs – as a public health imperative for which the benefits far outweigh the cost.[45]

7.5.3 The Need for Timely, Accurate Forecasting

As described in Section 7.3, increasing the supply of current and future vaccines take significant time (several years) and investment to come on-stream. This puts enormous pressure on vaccine manufacturers to correctly estimate demand, requiring detailed forecasting analyses. While timely and accurate demand forecasting by government and public health officials is essential in securing adequate supply, it also permits tighter inventory control to minimize waste for all parties – both of which help to achieve the high-level goal of ensuring that the intended patient population receives recommended vaccines according to immunization program schedules. Accurate forecasting also allows for more timely vaccine delivery to designated users, including longer shelf-life (e.g. better expiry dating) on a per lot basis. In general, vaccine forecasting is a complex exercise as described below. In particular, generating precise estimates can be very challenging for newly approved vaccines, for which uptake and coverage rates within both the public and private sectors can be uncertain.[46]

Two commonly used methods for vaccine forecasting include estimates based on: i) target population; and ii) previous consumption.[47] The former method employs calculations based on assumptions regarding the target/eligible cohort, dosing, coverage rates, and vaccine wastage; such methods may also require adjustment to reflect actual need within the context of individual immunization programs (e.g. to allow for catch-up programs or outbreak situations in local jurisdictions). In contrast, methods based on previous consumption estimate historical usage, as well as average annual increases, to establish vaccine order thresholds for future years. Ideally, both methods should be utilized and compared, and any discrepancies in estimated dose requirements (e.g. greater than 5%) should be carefully evaluated to determine if waste, under- or over-vaccination, or erroneous assumptions are contributing factors that may result in excessive vaccine loss or over-purchasing.[48] Detailed assessment of this nature may also help to generate savings within a specific vaccine budget and/or spending plan. Interestingly, in the context of the current H1N1 influenza pandemic, a recent study in the journal Nature concludes that use of the worldwide Internet may make it possible to detect influenza epidemics in areas with large populations of web search users, i.e. by tracking influenza search queries.[49] Hence the Internet is viewed as an increasingly promising tool to provide real-time input assumptions in developing forecasting models for flu pandemics – and potentially, in projecting vaccine requirements.

7.5.4 Cold Chain Management and Vaccine Stability

In addition to issues surrounding vaccine shortages and demand forecasting, other concerns regarding supply management also come directly to the forefront when vaccines are compromised by a breach in storage conditions and/or procedures. In this context, cold chain maintenance is defined to encompass the materials, equipment and procedures required to maintain vaccine temperatures (2°C to 8°C for most vaccines, –30°C to 5°C for some, as indicated in individual product monographs) while in transit throughout the distribution and storage process.[50,51] In general, cold chain maintenance is viewed as an essential, continuous, and cohesive set of practices to preserve vaccine stability, i.e. to ensure their availability and to maintain their effectiveness. Specifically, vaccine stability refers to the ability of the vaccine to retain its chemical, physical, microbiological, and biological properties within specific limits throughout its shelf-life.[52]

Cold chain management includes vaccine delivery from the manufacturer to/amongst the following sites: primary vendor sites (e.g. warehouse depots); public health units; pharmacies; and physician's offices (including transport by a patient to a physician's office), as well as appropriate storage and/or administration at each of these sites. Mechanisms for transport include refrigerated trucks and expedited air or ground shipments – modes of delivery that will ensure transit times are acceptable for maintaining the cold chain. Meeting cold storage requirements is particularly challenging in developing countries, where specialized networks, aircraft (helicopters), and equipment (such as kerosene or solar-powered refrigerators) are often required to support mass immunization campaigns.[53] The Public Health Agency of Canada (PHAC) has recently published a comprehensive guide that summarizes requirements for vaccine storage, handling and transportation, entitled "National Vaccine Storage and Handling Guidelines for Immunization Providers".[54] Additional resources are available through the PHAC website[55,56] and the U.S. Centers for Disease Control and Prevention (CDC).[57]

Critical attention is paid to cold chain management since temperature fluctuations or extremes can rapidly destroy many vaccines by diminishing potency and/or functionality of specific components (e.g. antigens or excipients), and may result in vaccine failure. A breach in the cold chain may also affect a vaccine's efficacy, or may increase the number of injection site reactions. Furthermore, cold chain disruptions may decrease shelf-life and can contribute significantly to waste – because compromised vaccines may need to be destroyed. Overall, to protect the (already fragile) vaccine supply, and to maximize the stability, potency and efficacy of each vaccine, it remains imperative for all parties to be diligent in maintaining the cold chain throughout the procurement, handling and supply chain processes.

Currently, manufacturers take extraordinary measures to ensure temperature excursions (outside recommended storage conditions) do not occur during product labeling, packaging and shipment. Yet cold chain management is considered vulnerable to disruption by factors outside the manufacturers' control, i.e. at regional or local levels of distribution, or during unexpected ice storms or other widespread power failures.[58] Although most temperature-sensitive vaccines are maintained well within the required cold chain parameters, a key question that persists for both vaccine manufacturers and designated users is how to appropriately handle vaccines that have undergone brief temperature excursions. For example, if recommendations specify that a vaccine should be stored in the refrigerator at 2°C to 8°C, what should happen if the vaccine is stored unintentionally for one hour at room temperature, or for six hours at 15°C? Since exposure to temperatures outside the recommended range may not necessarily render vaccine failure – and in many cases, the vaccine can still be safely utilized – it is important that appropriate guidance is sought to assess product integrity (first by consulting the product monograph, and potentially also by contacting the manufacturer directly) before concluding the vaccine is unusable.[59] Designated users should also label the vaccine and document the specific incident details,[vi] while maintaining the product under recommended conditions until consulting the manufacturer to assess potential vaccine usability. At present, these recommendations are not consistently followed, and this leads to considerable financial loss by vaccine companies (and missed opportunities to immunize target vaccinees with earmarked inventory),[60] since the product can be returned to the manufacturer if there is uncertainty regarding cold chain status and potential stability loss.

vi Particulars regarding the vaccine lot number, expiry date, incident date, temperature excursion details (including temperature range and exposure time), as well as corrective measures, should be clearly documented.

Since 2007, BIOTECanada's Vaccine Industry Committee (VIC) has held several meetings with the Vaccine Supply Working Group (VSWG) of the Canadian Immunization Committee (CIC) – and more recently with other ad hoc task forces (representing the provinces and territories) and Health Canada's BGTD – to determine how industry can assist the government in minimizing waste due to unnecessary disposal of still stable, safe and effective vaccine that has experienced a cold chain breach.[61] Given the compelling need to educate all relevant stakeholders regarding cold chain issues, the VIC has proposed to work in partnership with the provinces/territories and the BGTD to provide available vaccine stability data to vaccine users as a key initial step, i.e. while continuing to use the product monograph as the principal guidance document for vaccine stability information. Vaccine manufacturers have considerable experience in assessing and managing product stability (and making recommendations on a case-by-case basis) and thus will continue to work collaboratively with regulatory authorities and designated users in all jurisdictions to improve cold chain and inventory management across Canada.

7.5.5 Distribution Channels

Another essential component of the Canadian vaccine supply chain is the underlying infrastructure for vaccine delivery, which relies on multiple distribution channels.[62,63] Since vaccine delivery for publicly- funded immunization programs is primarily administered by the provinces and territories,[64] manufacturers generally distribute vaccines to end-users by shipment from corporate facilities in Canada to provincial/territorial depots within the public health system. Vaccines are then shipped to regional or local health authorities, which in turn distribute product to individual health care facilities. Specifically, for publicly-funded programs, vaccines are administered mainly through provincial/territorial public health clinics and offices, physician-based practices, school-based clinics, hospital-based influenza programs, and elderly drop-in centres. In contrast, privately-funded vaccines are typically delivered from manufacturers' facilities to group purchasing organizations and/or individual health care providers at pharmacy-based clinics, travel clinics, or physician-based practices. For most vaccines currently on the market, it takes several months from final manufacturing steps (including lot release) to delivery to the end-user.[65]

As discussed in Paper 8, key vaccinators in Canada include physicians (frequently general practitioners and pediatricians),[66] pharmacists,[67,68] and nurses,[69] all of whom play a vital role in both vaccination and education within the current immunization delivery environment. As the ultimate end-users, target vaccine recipients encompass many segments of the general public, including infants, adolescents, adults/seniors, and other high-risk or special populations, such as international travelers, employees exposed to occupational hazards, and police/military personnel.

At present, vaccine program delivery costs (as distinct from vaccine acquisition/procurement costs) are generally not well tracked or understood by the provinces and territories. Delivery costs incurred by individual jurisdictions may include, for example, expenses related to intra-jurisdictional delivery; health care personnel; clinic overhead; syringes, needles and other consumables; and educational programs (including additional educational materials not already provided by manufacturers). Indeed, the need to explicitly assess delivery costs as unique, significant expenses within the broader context of vaccine program implementation has been identified as a key challenge by stakeholders attending the 2008 International Forum on National Immunization Programs, as convened by the PHAC.[70] Moreover, determining appropriate methods for assessing delivery costs – and finding funding to execute such evaluation – will represent additional requisite challenges.[71]

7.6 Canada's Vaccine Procurement Environment

On the whole, procurement procedures for purchasing vaccines in Canada are complex and cumbersome, and in certain cases, geographically fragmented. Essentially, after overcoming the significant research, regulatory, recommendation and financing challenges currently faced by vaccine developers (summarized in Papers 3, 4, 5 and 6, respectively), manufacturers must also engage in competitive contract negotiations as one of the final major steps prior to supplying/delivering vaccines to Canadians. Within Canada's current vaccine procurement framework, these negotiations represent another hurdle above and beyond the scrutiny of other government bodies, including Health Canada's BGTD, the National Advisory Committee on Immunization (NACI), the Canadian Immunization Committee (CIC), and the provincial/territorial (P/T) advisory committees that make decisions to provide vaccine financing. While funding for most vaccines is committed primarily through P/T public health budgets, funding for five specific vaccines has also come through time-limited federal funding since 2003,[72] i.e. via transfer payments from federal trust funds (see Paper 6, Section 6.3.2). These funds are then used by individual jurisdictions to purchase vaccines by establishing contracts with vaccine suppliers. Overall, the challenges and intricacies of the current vaccine procurement process add yet another layer of complexity to the Canadian vaccine landscape – both in terms of introducing new vaccines, and maintaining consistent supply of existing vaccines.

7.6.1 Federal Bulk Purchasing Program and Other Procurement Mechanisms

Prior to the introduction of the National Immunization Strategy (NIS) in 2003, as summarized in Paper 5, a federal bulk purchasing program – led by Public Works and Government Services Canada (PWGSC) – provided the key mechanism for procurement of publicly-funded vaccines.[73] Within this program, annual contracts were awarded on a "product by province" basis, in which provinces retained the right to select specific vaccines based on unique jurisdictional public health needs, and thus were not limited to selection based on lowest vaccine price. Notably, within this framework, different provinces could potentially choose to purchase different vaccines that target the same disease.[74] Apart from this initial federal bulk purchasing program, provincial contracts (between sole-source supplier and individual provinces) and provincial tenders (based on multiple suppliers) also existed prior to the NIS, although the latter were relatively rare.

Subsequently – and as one of the key components within the broader NIS mandate – specific objectives for enhancing vaccine procurement were identified in terms of achieving the best value for vaccines, and ensuring the security and quality of Canada's vaccine supply.[75] Within this context, the VSWG was formed as a centralized working group to support the CIC; part of the VSWG mandate was to represent the provinces/territories (P/Ts) in making vaccine purchasing decisions and specifying contract terms and conditions.[76] Thus, since the introduction of the NIS, the PWGSC has acted as an agent of the VSWG to manage vaccine tenders/contracts on behalf of the provinces and territories.[vii] A key feature of the "new" federal/provincial/territorial (F/P/T) bulk purchasing program, as introduced under the NIS, included a move toward "one system for all jurisdictions", in which P/Ts would forgo the right to select specific vaccines for their individual needs. As such, all jurisdictions would need to reach consensus (bound by a formal Memorandum of Understanding) regarding a single vaccine for each targeted disease, and price became the key differentiator.[77] In general, this type of tender process is based on a "winner take all" strategy, in which all sales (across all jurisdictions) for a given vaccine are awarded to the lowest price bidder.[78]

vii In administering the vaccine procurement process on behalf of the VSWG, the PWGSC is responsible for issuing and evaluating tenders, signing contracts, and post-award contract maintenance (including evaluation of contract compliance and administering any penalties).

As the PWGSC/VSWG bulk purchasing program evolved, a general trend was observed toward the implementation of dual-supplier (split) contracts, in which up to two suppliers provide the required vaccine doses for all regions, with individual market shares being determined via a competitive bidding process. Notably, dual awards can only be implemented when immunization advisory committees consider competitor vaccines (from different suppliers) similar enough to be fully "interchangeable".[viii] This system was based on the premise that dual awards would promote security of the vaccine supply by permitting market access to more than one supplier. From the purchaser's perspective, a key ramification of such dual awards was that P/Ts would forgo their option to select individual vaccines to meet their specific public health needs – in return for security of vaccine supply, as well as increased competition and anticipated lower prices.[ix] Specifically, detailed rules and calculations for awarding split contracts would be laid out in the contract evaluation/determination criteria (see example below).[79] At present, vaccines targeting influenza, meningococcal C, varicella, and measles, mumps, rubella (MMR) are typically purchased in Canada through dual tender/contract negotiations.

> Example: In a dual award situation, the tender may specify that the lowest price bidder will be awarded a contract as follows:
>
> - 60% (of required vaccine quantities) if the price difference (D) between the two lowest bidders is less than 20%, i.e. 60% if [D < 20%];
> - 65% if [21% ≤ D ≤ 30%]; and
> - 70% if [D > 31%].
>
> In this "sliding scale" example, the second lowest bidder would be awarded a contract for the balance of vaccine quantities, according to the price difference (D).

It should be noted that tender evaluation criteria may also specify that if the price difference between two bidders is greater than a given percentage (e.g. D > 40% in the example above), then the entire contract (100%) can be awarded to the lower priced bidder. Therefore, although security of supply is a stated priority, the designated users represented by the PWGSC/VSWG may (frequently) still choose a sole supplier, which implies the purchasers may not be willing to pay for the marginal cost of dual suppliers. Indeed, it has been suggested by jurisdictional representatives that while dual-source awards provide stability, single-source contracts tend to save money overall.[80]

Table 7.2 presents key features of the current F/P/T bulk purchasing program – within the broader context of other procurement systems in Canada – including direct contracts between individual P/Ts and vaccine manufacturers, and private sector mechanisms. Overall, the vaccine procurement process is intended to ensure that equal consideration is given to all eligible vaccines that meet the stringent requirements for regulatory approval in Canada.[81] The typical steps undertaken as part of the general procurement process are described below, with the vast majority of negotiation between suppliers and designated users (and/or administrators) being conducted through official documentation, rather than through meetings or other personal interaction.

viii In this context, "interchangeable" means similar enough (for the purposes of PWGSC/VSWG tenders) to satisfy total dose requirements, according to a specified ratio of market shares (e.g. 60% + 40%), in targeting a given disease.

ix As an example, for a 60%/40% dual-supplier award, certain jurisdictions (representing ~60% of required doses) would receive vaccine from the first manufacturer, whereas other jurisdictions (accounting for the remaining 40% of total requirements) would receive vaccine from the second manufacturer. The decision regarding which jurisdictions receive which vaccine is made by the PWGSC (and hence is not based on clinical or epidemiological considerations, since competitor vaccines are deemed interchangeable); it is not based on the preferences of individual jurisdictions.

Table 7.2 – Vaccine Procurement Mechanisms in Canada [82,83,84,85]

Procurement System	Key Features
Publicly-Funded Vaccines	
F/P/T Bulk Purchase Program (coordinated by PWGSC on behalf of VSWG)	• Almost all P/Ts currently purchase the vast majority of their vaccines through the bulk purchase program • P/Ts pay the federal government to administer services provided by PWGSC • PWGSC/VSWG collaboration includes representatives from all P/Ts (including Québec), as well as from the PHAC and BGTD • Collectively, these groups (particularly PWGSC) provide significant expertise in procurement systems/contracts and supply chain logistics • VSWG contributes additional expertise in immunization program development, scientific and clinical affairs, and vaccine inventory management (including participation by physicians, nurses and other immunization experts) • For most vaccines (with the exception of influenza), Québec makes vaccine procurement decisions independently of the F/P/T collaborative, i.e. as administered through Approvisionnements – Montreal (see website at www.aqesss.qc.ca/fr/associes.aspx?sortcode=1.18.20.21); Quebec may specify unique contract terms and conditions (e.g. no split contracts or returns) [For influenza vaccines, PWGSC coordinates contracts on behalf of all jurisdictions, including Québec] • The F/P/T program is not mandatory, thus individual jurisdictions may opt out (without legal implications) for the purchase of specific vaccines; for example, B.C. opted out of the F/P/T program to purchase its pneumococcal conjugate vaccine needs in 2009 (which it purchased through a direct contract with the B.C. government Provincial Health Services Authority) • Contract awards may be “winner take all” or (more recently) “dual-supplier”
Direct Contracts (between individual jurisdictions and vaccine suppliers)	• P/Ts can use procurement vehicles within their own jurisdictions to purchase vaccines directly from manufacturers on a competitive/noncompetitive basis • Individual contract organizations, e.g. in B.C. and Quebec (see websites at www.bcbid.gov.bc.ca/open.dll/welcome and www.seao.ca/index.aspx) also oversee procurement/contracts for other industry sectors; they may have less vaccine-specific expertise and be more “at arms length” from immunization stakeholders – and hence may be more likely to view vaccines as commodities • P/Ts that utilize direct contracts are not required to pay administration fees to PWGSC, but must weigh this benefit within the context of potential losses in bulk purchasing power (i.e. for significantly smaller volume requirements),although a typical contract clause is to secure the “lowest price in Canada”

Procurement System	Key Features
Privately-Funded Vaccines	
Private Sector Purchases	• Private sector vaccine procurement mechanisms are generally more fragmented and less well characterized (versus public sector procurement systems) • Procurement procedures are typically established within the context of private/ employer drug benefit plan policies • Private sector vaccine purchases (e.g. primarily travel vaccines) are usually administered through group purchasing organizations on behalf of individual pharmacies, clinics, or other physician-based practices • Purchase volumes are relatively small, and hence buyers may be unable to exercise bulk purchasing power and/or negotiate price discounts

To initiate the procurement process, i.e. following the approval of a specific immunization program by a given jurisdiction (or private provider), vaccine requirements are typically estimated based on market research and appropriate forecasting methodologies (see Section 7.5.3). Designated users (represented by the PWGSC/VSWG, individual P/Ts or group purchasing organizations) then issue a "call letter" (request for proposal, or "RFP") to solicit bids by potential suppliers. Manufacturers usually must respond within a short turnaround time (e.g. two to three weeks), and an announcement is then made regarding the results of the contract award, potentially within another one to four week period. Delivery of the first shipment of vaccines to designated users may then occur as soon as four weeks following the award notification, depending on the signing of the final contract and the specified delivery schedule.

7.6.2 Key Industry Concerns: Vaccine Perceptions, Pricing and Wastage

While Canada's vaccine procurement policy environment is complex and multi-faceted (with a diverse range of purchasing structures), several common themes emerge regarding its current limitations and impact, many of which are cause for concern among vaccine manufacturers. First, Canada's current vaccine procurement framework essentially treats vaccines as low-tech commodities; the present system does not adequately recognize vaccines as technology-intensive products (requiring long production lead times and a highly trained human resource base) with proven value in disease prevention. Second, within the public sector, the current procurement system is largely driven by P/T budgets, and is centralized through the VSWG. Hence the public market for vaccines is considered a monopsonistic marketplace, in which the government acts as a single powerful buyer with significant bulk purchasing power, ultimately placing downward pressure on price. This primary focus on price has driven vaccine prices in Canada to among the lowest in the developed world[86] – and consequently, has reduced vaccine industry profit margins,[87] while continuing to discourage potential new entrants from supplying the Canadian market (and/or building Canadian manufacturing facilities).

It should be noted that for patented vaccines, the Patented Medicine Prices Review Board (PMPRB)[88] acts as yet another regulatory force to exert downward pressure on vaccine prices (see Paper 6).[x] Hence for patented vaccines, the PMPRB and the current F/P/T bulk purchase program act in synergy to ratchet vaccine prices downward. In addition, in the context of the competitive tendering process, vaccines with patent protection have no defined period of market exclusivity (i.e. no true period of suspended competition), since vaccines that target the same disease (e.g. meningococcal C)[xi] may be considered interchangeable for the purpose of competitive bids, regardless of potential differences in safety and efficacy profiles. This situation stands in sharp contrast with that for other patented pharmaceutical drugs and biologics, for which distinct product profiles are acknowledged, and differential pricing is indeed permitted for therapies that target/treat the same indication. Also, for other patented drugs, another key distinction (compared to vaccines) is that the decision to select one specific drug versus another (for a given indication) occurs at the point of the individual prescription, based on individual patient needs, physician preferences, and prevailing reimbursement guidelines. In contrast, vaccines that target the same indication must compete in the marketplace at the point of F/P/T bulk purchasing decisions – again more like "wholesale" commodities – almost exclusively based on price.

Overall, from the manufacturers' standpoint, a key concern regarding Canada's current procurement system – and broader PMPRB policy environment – is that the strong price emphasis fails to recognize other important social values and business principles. For example, stronger vaccine pricing in industrialized countries is typically viewed as an effective means of subsidizing lower pricing in the developing world, i.e. by allowing individual manufacturers to offer differential (or preferential) pricing.[89] Thus, suppressing vaccine prices in Canada is counterproductive within the global context – by limiting Canada's contribution to keeping vaccine prices reasonable for the world's poorest nations.

Furthermore, the recent price erosion observed within Canada's vaccine procurement framework is believed to have stifled innovation within the research community, and as such, vaccine purchasing policies may be viewed as hindering the development of future life-saving vaccine technologies. Specifically, current procurement policies do not adequately recognize the value of vaccine discovery and clinical research, including the millions of dollars invested in R&D by Canada's vaccine manufacturers each year, which contribute directly to economic growth and future prosperity.[90] Therefore, by treating vaccines as commodities, the current Canadian vaccine procurement framework may result in missed opportunities to create novel vaccines, as well as to foster emerging companies and future employment.[91] In contrast, assuming more favourable vaccine procurement policies and pricing incentives were indeed in place, Canadians could tap into the benefits of enhanced investment in R&D, and a more robust job market and corporate tax base – even if the vaccines produced in Canada were exported internationally. In summary,

x Within Canada's current vaccine procurement framework, vaccine prices are determined primarily by the competitive tender and negotiation process. In addition, for patented vaccines, the PMPRB will not allow prices beyond an "excessive" threshold at launch, and will not allow annual price increases above a specified level, according to detailed PMPRB pricing regulations. Thus for patented vaccines, prices tend to be driven down by both competition and international prices – and then subsequently remain low, primarily due to PMPRB pricing control.

xi Three meningococcal C vaccines are currently licensed in Canada: NeisVac-C, Meningitec, and Menjugate. (Menactra offers additional protection, i.e. to meningococcal disease-causing serotypes A, C, Y, and W-135.)

policy makers must not overlook the fundamental role played by procurement policy (and appropriate pricing incentives) in fostering a positive domestic market environment, promoting continued innovation in vaccine technology, and enhancing Canada's contribution to global health.[92,93,94,95]

Apart from the pressing issues surrounding the perception of vaccines as commodities and recent erosion of vaccine prices, other parameters within the current procurement environment may also have serious drawbacks; these factors pertain to contractual design and/or obligations – and can contribute directly to vaccine waste (see Table 7.3 regarding contract-related challenges within Canada's vaccine procurement framework). For example, such factors (including certain mandatory requirements) may include one or more of the following constraints: i) insufficient lead time for initial vaccine delivery, optional contract extensions, and optional quantities; ii) mandatory return policies[xii]; and iii) the lack of appropriate/specific cold chain clauses, i.e. which ideally, should take into consideration information in the product monograph and any supporting stability data, if available. Unfortunately, constraints of this nature tend to encourage (rather than actively reduce) vaccine waste. Since vaccine manufacturers must absorb the cost of vaccine wastage, the current procurement system ultimately increases overall production costs and decreases total production capacity.

More importantly, from a public health perspective, vaccine waste is associated with the opportunity cost of missed vaccination for individuals in other jurisdictions, who may go without the benefits of immunization. Moreover, since global demand for vaccines exceeds global supply, both industry and government players have a shared responsibility and moral obligation to protect international vaccine supplies by minimizing vaccine waste. Indeed, over three million children in underdeveloped countries die every year because they are not reached with basic vaccines; to help satisfy such unmet needs and ensure the success of immunization programs worldwide, Canada must do its part to reduce waste and to help prevent a crisis in global vaccine supply.[96]

In moving towards the high-level goal of improving inventory management and reducing vaccine waste – particularly within the context of the public (PWGSC/VSWG) vaccine procurement environment – BIOTECanada's VIC has held several meetings (and shared detailed correspondence) with the VSWG, with increasing frequency since 2005. Specifically, the VIC has recently proposed several recommendations in terms of developing mutually agreeable contract terms for improved vaccine procurement (refer to Table 7.3), including greater lead times pertaining to supply and demand decisions, enhanced forecasting and product utilization (e.g. through improved cold chain management and reduced need for vaccine returns), as well as reasonable penalties for unavoidable supply disruptions.[97] At present, many of these critical issues remain unresolved.

While Table 7.3 highlights the major themes regarding procurement contract limitations that require immediate action to help promote a secure vaccine supply, the VIC has also compiled a lengthy, confidential list of additional recommendations regarding specific contract terms and clauses (based on the current format of a standard/generic RFP); the current status of these discussions fall outside the scope of this paper. In general however, since each vaccine is unique, the details regarding capacity constraints, procurement lead times, package requirements, shelf-life and wastage will vary with the specific product (or sub-class of vaccine that targets a given disease). Hence for each competitive bid situation, customized procurement evaluation criteria and clauses are likely to be required in developing the finalized contract, ideally taking into consideration the intended immunization program, individual product(s), production lead times, regulatory issues, and product demand patterns.[98]

xii Technically, vaccine returns may include: i) indated product that is not utilized; ii) outdated product that has expired; and iii) product that has undergone a temperature excursion.

Table 7.3 – Contract-Related Challenges Within Current Procurement Framework (PWGSC/VSWG) [99,100]

Current Contract Design (Sample Terms & Conditions)	Impact on Manufacturers & VIC Recommendations
Contractual obligations (mandatory requirements) may include, for example: (i) imminent delivery dates [e.g. first delivery within 30 days of awarding contract]; (ii) optional contract extensions [e.g. + 1-2 years after first year(s)]; (iii) optional quantities [e.g. 80-120% of required doses]; (iv) minimum expiry dating [e.g. 12 months from delivery] [These clauses impact anticipated demand *prior* to shipment by manufacturer.]	a) Short notice (≤ 1 month) for initial vaccine delivery (i), or 1 day notice for optional periods of supply (ii) may be given; this is extremely difficult for manufacturers to accommodate, given long production lead times. b) Manufacturers must also make available maximum order quantities, e.g. 120% for (iii), regardless of actual quantities delivered – and paid for. c) The net result is that manufacturers must be ready to provide vaccine [e.g. ~40% of estimated doses for (iii)] that ultimately may not be required by the designated user, thus significant doses of vaccine (already labeled for use in Canada) may never be shipped to the intended user. Vaccines must re-packaged and labeled for potential use in other countries, and expiry dating will also be diminished for other contracts (see iv). d) Overall, current contract requirements contribute directly to vaccine waste. **VIC Recommendations:** 1) Users should allow sufficient lead time (six months minimum) for initial delivery, contract extensions, and volume increases for optional quantities, i.e. to ensure manufacturers can adjust supplies to meet global demand. 2) To encourage more accurate forecasting and optimal product utilization, users should be required to pay for min quantities, regardless of usage.
Minimum return policies (typically also a mandatory requirement) [e.g. the purchaser has the right to return 5% of purchased vaccine *after* shipment; i.e. typically due to expiry at local centres/clinics]	a) Returned doses of vaccine contribute significantly to product waste. b) More liberal return policies have been observed to be associated with greater waste. **VIC Recommendations:** 1) The VIC is committed to working collaboratively with VSWG to reduce the need for vaccine returns, i.e. by encouraging use of methods to ensure that vaccine quantities ordered are indeed utilized.

Current Contract Design (Sample Terms & Conditions)	Impact on Manufacturers & VIC Recommendations
Lack of customized cold chain clauses for individual vaccines [e.g. clauses that specify how to handle product that has undergone temperature excursion *after* shipment by manufacturer]	a) Vaccines not maintained under recommended cold chain conditions (typically 2-8°C) can be returned to manufacturer; this is an additional (and frequently unnecessary) cause of vaccine waste. b) End-users may not seek guidance to assess product integrity (i.e. by consulting the product monograph and/or contacting the manufacturer) before returning the vaccine; manufacturers may not have adequate opportunity to provide supporting stability data. **VIC Recommendations:** 1) Cold chain clauses should be adjusted according to shipping/storage conditions outlined in the product monograph (specific to each vaccine). 2) Users should be required to maintain product under proper cold chain conditions until consulting the manufacturer to determine product status.
Penalties for inability to supply	a) If the manufacturer is unable to supply adequate vaccine, the vendor may be obliged to pay for the difference from an alternate supplier. **VIC Recommendations:** 1) The contract should limit financial liability (maximum penalty) to the amount specified in the contract during the period of inability to supply. 2) The manufacturer should be allowed to terminate a contract with six months notice (in the case of a long-term interruption); this should give reasonable lead time to designated users to find an alternate supplier(s) without imposing crippling penalties.

7.6.3 The Need For Partnerships in Achieving Optimal Procurement Systems

Given that Canada's current vaccine procurement framework is not conducive to a favourable investment or business environment, the need to explore alternative procurement methods has been proposed by vaccine manufacturers.[101] Indeed, other procurement mechanisms that focus on supply chain value efficiency do exist[102,103] and are based upon collaborative relationships between vaccine suppliers and purchasers/users that seek to align shared objectives in satisfying public health needs. Notably, at the recommendation of Canada's vaccine manufacturers, the PHAC has taken initial steps to evaluate other vaccine procurement systems, i.e. during the International Forum on National Immunization Programs held in December 2008. During this Forum, representatives from eight "higher income" countries[xiii] presented governance structures for immunization programs (including vaccine funding and procurement mechanisms) for the purpose of identifying key lessons and best practices that merit consideration in the Canadian context.[104] Information gained from the Forum was intended primarily to stimulate new ideas and broaden current perspectives; the PHAC has not provided further updates regarding future direction or immediate next steps.

Since vaccine procurement in Canada is a shared responsibility across manufacturers, federal government agencies (PHAC, PWGSC/VSWG) and provincial/territorial public health authorities, it remains imperative that all stakeholders continue to work in collaborative partnership to further improve procurement policies, i.e. through appropriate negotiation and procurement reform. Ideally, an optimal, modern procurement system would foster: i) fair pricing structures that reflects the full value of vaccines; ii) reasonable lead times, to permit vaccine production and capacity building (including improved program planning and demand forecasting); and iii) enhanced vaccine inventory management, i.e. through optimized vaccine storage and handling, thus minimizing product waste. Continued progress towards a revitalized and transparent procurement process is hoped to promote greater alignment between the interests of public health immunization programs and the broader capabilities of the vaccine industry – particularly in terms of building a more stable immunization system for all Canadians, in which patients have timely access to innovative vaccines. Ultimately, the collective, cooperative efforts of manufacturers, F/P/T governments and other purchasers will be required to secure a more reliable, robust supply of existing and novel vaccines to maintain the health of the Canadian population.

xiii Participating countries included Australia, Austria, Belgium, Germany, Spain, Sweden, the United Kingdom and the United States.

7.7 Recommendations

Over the past several decades, vaccines have demonstrated tremendous value in eradicating smallpox, eliminating major disease outbreaks, and preventing thousands of deaths annually worldwide. These successes can be attributed to partnerships between the private vaccine industry and aggressive public health programs that target children, adolescents, and adults.[105] Yet these recent successes in global disease prevention are being threatened by persistent (and increasing) difficulties in balancing vaccine demand and supply, and – particularly in Canada – by additional constraints imposed within the current vaccine procurement framework. Simply put, within the context of an already fragile vaccine supply, Canada's current vaccine procurement system does not appear to make good business, ethical, or practical sense, particularly given the primary price focus and existing tolerance for vaccine waste.

Overall, vaccine manufacturers and all partners in immunization must work towards improving the effectiveness and efficiency of vaccine procurement systems for the benefit of Canadians, i.e. by creating an environment conducive to meeting both industry and public health objectives in implementing immunization program strategies. Ideally, an alternative procurement system must recognize the need for a secure vaccine supply, promote the benefits of vaccine innovation and future investment, and focus on reasonable price for best value – acknowledging vaccines as unique, highly technical products, rather than commodities. Although VIC discussions with the VSWG have yielded positive results to date, a great deal of collaborative work remains ahead, i.e. to achieve the common goal of streamlining the process for making high-value vaccines available to patients as ultimate end-users. Hence BIOTECanada's VIC remains committed to working jointly with the PWGSC, VSWG, PHAC and BGTD to develop a procurement framework that ensures access to a safe and secure supply of vaccines for all Canadians. In the spirit of such collaboration, the VIC has put forward the following recommendations (several of which are introduced in Table 7.3) for consideration by key federal, provincial and territorial government stakeholders.

Federal/Provincial/Territorial (F/P/T) Recommendations

1. In view of long production lead times, and the complex, costly, and highly regulated nature of the vaccine manufacturing environment, policy approaches to developing an efficient vaccine marketplace should encourage long-term investment in Canadian-based innovation, R&D and manufacturing capacity within the vaccine sector. Such initiatives should assist in preventing manufacturers from exiting the vaccine market, and ensuring continued supply of existing and cutting-edge vaccines (see also Paper 3).
    - Investment incentives may include both “push” mechanisms to reduce the cost burden of vaccine R&D and production (including government grants and tax rebates), and “pull” strategies (such as advanced purchase agreements and strategic purchasing) to increase demand volume or to enhance product prices.
    - The recent H1N1 influenza pandemic underscores the need to protect and build long-term capacity of the vaccine supply, i.e. to help protect Canadians from current/future threats, including emerging diseases and/or bioterrorist attacks, which are a threat to global and national security.

2. Regarding vaccine pricing, increased recognition is required by designated users regarding the true value of the vaccine supply chain – and that lowest price does not necessarily deliver greatest value.
    - Implementation of more favourable pricing structures for vaccines (including appropriate tender-based evaluation criteria and flexibility in contract terms) could stimulate the economy by encouraging R&D to create innovative vaccine products, while fostering future job creation and a more robust tax revenue base. Enhanced pricing structures would more appropriately reflect the full value of vaccines as high-technology products, rather than mere commodities in health care.
    - Pricing barriers that stand in the way of competitive market profitability (including strict PMPRB regulation of patented vaccines; see also Paper 6) should be removed, or undergo reform, to help strengthen the vaccine enterprise, i.e. by encouraging companies to continue to risk investment capital to build future production capacity.
    - Appropriate pricing structures could also foster the development of new technologies and manufacturing models (e.g. based on recombinant methodologies or disposable bioreactor systems) to decrease future vaccine production timelines and costs.

3. In working towards an optimal, modern, fair and transparent vaccine procurement system, the following revisions should be made to specific terms and conditions in improving current PWGSC/VSWG contract design (and ideally also for direct contracts with individual jurisdictions, where appropriate).
    - With regard to contractual obligations (e.g. mandatory requirements):
        i. Users should allow sufficient lead time (six months minimum) for initial delivery, contract extensions, and volume increases for optional quantities, i.e. to ensure manufacturers can adjust supplies to meet global demand.
        ii. To encourage better program planning and more accurate demand forecasting, users should be required to pay for minimum quantities, regardless of usage.
    - With respect to minimum return policies:
        i. The VSWG should work in close cooperation with the VIC to reduce the need for vaccine returns, i.e. by developing methods to ensure that vaccine quantities ordered are indeed utilized.
    - With regard to cold chain supply management, policies and procedures should also be put in place to educate and monitor relevant stakeholders/users regarding storage and handling requirements, with the goal of mitigating losses due to vaccine waste.
        i. Cold chain clauses should be adjusted according to shipping/storage conditions outlined in the product monograph (specific to each vaccine).
        ii. For vaccines that have undergone a temperature excursion (outside recommended storage conditions), users should be required to maintain the product under proper cold chain conditions until consulting the manufacturer to determine product status.
    - In the event of inability to supply vaccine:
        i. The contract should limit financial liability (maximum penalty) to the amount specified in the contract during the period of inability to supply.
        ii. The manufacturer should be allowed to terminate a contract with six months notice (in the case of a long-term interruption); this should give reasonable lead time to designated users to find an alternate supplier(s) without imposing crippling penalties.

4. To ensure the effectiveness, efficiency, value and success of Canada's publicly-funded immunization programs, continued efforts are required to further improve and enhance Canada's vaccine procurement system by building collaborative partnerships across key stakeholders (including manufacturers, federal government agencies, provincial/territorial public health authorities and academia).
    - The VIC has proposed to establish a dedicated working group (including representatives from the PHAC, VSWG, provinces/territories, BGTD and industry) to address supply chain management issues, with particular emphasis on strengthening terms and conditions pertaining to vaccine forecasting and procurement lead times, cold chain requirements and product stability data/guidelines.
5. Continued efforts should be made by F/P/T policy makers to explore and consider alternative vaccine procurement systems currently in place in other developed countries, i.e. to identify key lessons and best practices that merit consideration in the context of the current Canadian vaccine landscape.

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BIOTECanada
130 Albert Street #420
Ottawa, ON K1P 5G4
613-230-5585
www.biotech.ca