Chapter 26

Health Canada

Regulatory Regime of Biologics

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Main Points

26.1 Our audit of Health Canada's regulatory regime for biologics found that the Department is taking a reasonable approach in developing and implementing frameworks and approaches for regulating different biologics (blood and blood products, cells, tissues and organs of human or animal origin, vaccines and other biological drugs). Our work focusses on the management of the regime for regulating biologics. Therefore, we did not conclude on the effectiveness of specific regulations or on the safety of specific products.

26.2 The Department faces important challenges. It needs to do the following:

- to establish more formal guidance to determine the most appropriate regulatory approach for a given situation;
- to maintain the currency of regulations;
- to obtain sufficiently qualified staff to deal with the rapid technological advances in biologics; and
- to implement sufficient databases to adequately process, analyze and disseminate information on adverse reactions and events.

26.3 Overall, we found that the Department has adopted a proactive approach to identifying risks that could threaten the health and safety of Canadians in the area of biologics. Though the science for xenotransplantation (the use of live, non-human animal cells, tissues and organs in humans) is not perfected, the Department is being proactive in planning a regulatory regime for xenografts. However, many delays have characterized the implementation of the regulatory regime for transplantation of human tissues and organs. Transplants of these types have been performed in hospitals for a number of years.

Background and other observations

26.4 Health Canada is responsible for regulating biologics under the provisions of the *Food and Drugs Act* and Regulations. Accordingly, the Department's objective is to ensure that biologics available to Canadians are safe, effective and of high quality. The Bureau of Biologics and Radiopharmaceuticals does much of this work with several other bureaus in the Therapeutic Products Directorate of the Health Products and Food Branch. As well, the Population and Public Health Branch conducts some surveillance activities.

26.5 The safety of biologics is an important aspect of public health. Rapid advances in science have resulted in increasing regulatory challenges. Many of the federal laws that govern health and safety were developed decades ago. Today, science is yielding new products that up until recently were unimaginable. Some products and practices carry potential health risks and raise difficult questions that current legislation may not be fully equipped to address. It is important that regulations remain current. It is also necessary to ensure that the tools required to put in place regulations — or other interventions — are also current and sufficiently flexible to deal with changing demands.

26.6 The Department follows a traditional approach with prescriptive regulations to regulate most biologics. This framework is well-established and offers some benefits. However, Health Canada believes that the framework is not sufficiently flexible to deal with emerging products and other technological advances in

biologics. Therefore, the Department is moving toward adopting a standards-based regulatory approach for blood, tissues and organs, and xenografts. Under this approach, third-party standards development organizations develop standards with Health Canada and other interested parties.

26.7 The Processing and Distribution of Semen for Assisted Conception Regulations (the Semen Regulations) represented the only regulatory framework in biologics that incorporated by reference in the Regulations standards developed by a third party. While this approach appears to offer some benefits including more flexibility to deal with rapid changes in technology, there are some important issues that need to be addressed. The Department needs to ensure that compliance is verified and that accountability is assured for regulations referencing its own technical standards. The Department needs to apply lessons learned from the implementation of the Semen Regulations to future standards-based regulatory frameworks, as applicable.

Health Canada's responses to our recommendations are included in this chapter. The Department agrees with the recommendations and indicates the actions that it is taking or intends to take to address them.

Introduction

A wide range of safety risks are associated with biologics

26.8 In recent years there has been significant public interest in the safety of biologics, which include blood and blood products, cells, tissues and organs of human or animal origin as well as vaccines and other biological drugs. (Exhibit 26.1 presents examples of commonly known biologics.) This interest has been demonstrated by the 1993 report of the Royal Commission on New Reproductive Technologies, the 1997 final report of the Commission of Inquiry on the Blood System in Canada (Krever Commission) and the 1999 Report of the Standing Committee on Health on Organ and Tissue Donation and Transplantation.

26.9 Unlike pharmaceutical drugs that are manufactured from chemical sources, biologics are produced from biological or "living" material, that is, material from humans, animals or micro-organisms. In particular, there is a greater variance in the components of biological products than in those of chemically derived products. Hence, there is a wide range of safety risks associated with biologics. Some of the risks are known, such as risks associated with the transmission of infectious diseases, transfusion reactions and bacterial contamination. However, others are not as well understood or are emerging risks associated with the transmission of unknown infectious agents. Examples of the agents include animal viruses, new variant Creutzfeldt-Jakob disease and the transmission of malignant disease.

26.10 The impact that biologics have on Canadians is both highly individualized and far-reaching. There are some 350 biological drugs approved for sale in Canada, of which about one third are vaccines. A significant proportion of these products are considered to be leading-edge technology and of particular interest to persons who face life-threatening and seriously debilitating illnesses. This fact is evidenced by the proportionately higher percentage of priority reviews of biological drugs than of pharmaceutical drugs. In 1998, 1,564 kidney, liver, heart and lung transplants occurred, but there was a considerably higher demand for organ transplants. While the technology for transplants of tissues (such as cornea, skin and bone marrow) is increasing, statistics on their frequency are not readily available. Each year approximately 3,500 Canadian women obtain donated semen for assisted conception, and many thousands of Canadians receive blood and blood products. In 1999 Canadian Blood Services and HÉMA-QUÉBEC collected about 920,000 units of whole blood.

26.11 With the recent advances in science and reproductive technologies, it is expected that there will be a significant growth in new biological products and therapies, such as xenografts (the use of live, non-human animal cells, tissues and organs in humans), gene therapy and stem cell therapy. Xenotransplantation, while controversial, is expected to gain from significant technological advances as the demand for human organs far exceeds their supply. These rapid developments require a regulatory regime that is up-to-date and responsive to change.

There is a wide range of safety risks associated with biologics.

It is expected that there will be a significant growth in new biological products and therapies. These rapid developments require a regulatory regime that is up-to-date and responsive to change.

Exhibit 26.1

Examples of Some Commonly Known Biologics

- Allergenic substances used for the treatment or diagnosis of allergic or immunological diseases
- Blood and blood derivatives
- Certain hormones and enzymes
- Insulin
- Semen
- Tissues: skin, eye cornea
- Organs: liver, heart, lungs
- Vaccines

Source: Health Canada

There are various approaches to regulating products

26.12 There are various instruments, like public education, voluntary guidelines, standards and regulations, that the government can use to ensure the safety of products available to Canadians. The development and application of regulations have generally followed either the traditional prescriptive approach or the more recent standards-based approach. Many government regulatory regimes fall somewhere in between these approaches by encompassing characteristics of both. The government is accountable for all its regulations, regardless of how they are developed and how standards are incorporated or referenced in regulations.

26.13 Regulations developed using the traditional prescriptive approach generally contain detailed product and manufacturing standards, which are written into the regulations themselves. Under this approach, the government leads the development of the regulations by following a prescribed regulatory process, which includes the requirement for a regulatory impact analysis statement. While the government does not necessarily seek the agreement of interested parties, it does consult them.

26.14 In 1996 the Treasury Board Secretariat launched the Standards and Regulatory Reform Program and encouraged all government departments to participate in developing standards-based regulatory regimes, where appropriate. Under this approach, standards development organizations develop standards with interested parties by following an accredited process based on consensus. The government may take part in developing the standards, but it is only one of several stakeholders comprising relevant industry representatives, professional bodies, technical experts and other interested parties. Where consensus cannot be reached easily it can considerably lengthen the regulatory development process.

26.15 Once the standards are approved and published, regulatory authorities may reference or incorporate them in whole or in part in the regulations, making them mandatory by law. Where standards are incorporated in or written into the regulations, they generally take on the characteristics of the traditional prescriptive approach because subsequent amendments must go through the prescribed regulatory amendment process. Where standards are referenced in the regulations, the relevant sections of the third party's standards document are named in the regulations and usually accompanied by the ambulatory phrase "as amended from time to time." For those to whom the regulations apply, the regulatory authority needs to make the referenced material available to them. Any subsequent changes to the standards are made by the standards development organization and are not subject to the prescribed regulatory amendment process.

26.16 In either case the regulatory authority maintains ultimate accountability for ensuring that the regulations are up-to-date. Under the traditional prescriptive approach, the government regularly reviews its regulations to ensure their ongoing relevance and currency and changes them accordingly. Under the standards-based approach, the government relies on the standards development organization to periodically review and update the standards document. The government may take part in this review as an interested stakeholder, but it cannot unilaterally change the organization's document. However, the government can change its own regulations and, as such, may elect to change the regulations' reference to the standards document in the event an agreement cannot be reached on proposed changes. Yet this alternative could also considerably lengthen the process.

26.17 Under both approaches, the regulatory authority often supplements regulations with policies, guidelines and operating procedures according to which manufacturers must meet certain requirements and submit to periodic inspections to ensure compliance. In addition, regardless of the adopted approach, the government is accountable for implementing the regulatory regime and establishing adequate compliance and enforcement systems.

26.18 Standards-based regulatory regimes are intended to provide greater flexibility than traditional prescriptive regimes when changes to the regulations are required quickly. Regulatory authorities have noted that traditionally, it can take up to two years to amend regulations according to established rules — by this time it can be too late to capture even further technological changes that have occurred. Standards-based regimes, which reference a third-party's standards document, are believed to be a quicker means for making amendments, provided that consensus can be reached in responding to new knowledge or technological advances. Proponents of standards-based regimes believe that they result in the following:

- the use of clearer and simpler language;
- more acceptance and greater compliance due to reduced need for education and enforcement because the standards are usually derived from consensus of all interested parties; and
- the harmonization of national standards with international standards.

Health Canada is responsible for regulating biologics

26.19 Under the provisions of the *Food and Drugs Act* and Regulations, Health Canada is responsible for regulating biologics. Accordingly, the Department's objective is to ensure that biologics available to the people of Canada are safe, effective and of high quality. The Bureau of Biologics and Radiopharmaceuticals, which carries out much of this work, is one of several bureaus in the Therapeutic Products Directorate of the Health Products and Food Branch. For 1999–2000, the Department estimates that it allocated to biologics $16.1 million and 157 full-time employees of the Therapeutic Products Programme. Additional resources were budgeted elsewhere in the Department, primarily for surveillance activities of vaccines and the Blood Safety Program.

Under the provisions of the *Food and Drugs Act* and Regulations, Health Canada is responsible for regulating biologics.

26.20 Other bureaus in the Directorate and other branches of the Department also share responsibility for biologics (see Exhibit 26.2). The Bureau of Compliance and Enforcement, whose activities play a role in regulating biological drugs, including vaccines, blood and semen, is building its technical expertise for organs,

Exhibit 26.2

Responsibility for Biologics at Health Canada

Health Products and Food Branch	Population and Public Health Branch
Therapeutic Products Directorate	**Centre for Infectious Disease Prevention and Control**
• Bureau of Biologics and Radiopharmaceuticals • Bureau of Compliance and Enforcement • Bureau of Policy and Coordination • Bureau of Licensed Product Assessments • Medical Devices Bureau	• Bureau of Infectious Diseases Blood-Borne Pathogens Division Immunization Division

Source: Health Canada

other tissues and xenografts. The Bureau of Policy and Coordination leads the development of policies, regulations and legislation and supports the various expert working groups. The Bureau of Licensed Product Assessments monitors reports of adverse drug reactions to licensed drug products, except immunization vaccines, which are the responsibility of the Division of Immunization in the Centre for Infectious Disease Prevention and Control, Population and Public Health Branch. The Division of Blood-Borne Pathogens conducts some surveillance, particularly of diseases that may be transmitted by blood. The Medical Devices Bureau tests and approves serological test kits used for the screening and diagnosis of infectious diseases.

Focus of the audit

26.21 We set out to determine how well Health Canada's regulatory regime is working in the regulation of biologics.

26.22 We present details on our audit's objective, scope, approach and criteria at the end of this chapter in **About the Audit**.

Overall, we found that Health Canada has adopted a proactive approach to identifying risks that could threaten the health and safety of Canadians in the area of biologics.

Observations and Recommendations

Regulatory Frameworks and Approaches

Health Canada is taking a proactive approach to identifying risks

26.23 Health Canada regulates biologics under the *Food and Drugs Act.* The purpose of the Act is to protect the health and safety of Canadians and enable the federal government to make regulations for carrying out the provisions of the Act. Given this mandate, we expected that Health Canada would adopt a proactive approach to identifying risks of biologics that could threaten the health and safety of Canadians.

26.24 In identifying risks, the Bureau of Biologics and Radiopharmaceuticals works closely with other bureaus, branches and organizations in Canada and abroad. As well, the Department maintains several expert advisory committees in this area. For example, the Expert Advisory Committee on Blood Regulation provides medical, scientific, ethical and communications advice on current and emerging issues concerning blood. There are also expert advisory committees on xenograft regulation and HIV therapies. In addition, the Department uses internal working groups such as the Steering Committee on Blood, Tissues, Organs and Xenotransplantation (BTOX), which acts as an advisory body, and the BTOX Policy Development Team, which is developing a risk management framework for blood, tissues and organs, and xenografts.

26.25 An example of the Department's proactive approach to identifying risks is the recent policy on variant Creutzfeldt-Jakob disease and the donation of blood and blood products by donors who have visited countries that present a higher risk of exposure to the disease. Health Canada took this strictly precautionary measure to reduce the theoretical risks of transmitting variant Creutzfeldt-Jakob disease (which is linked to mad cow disease) through the blood supply. The Department will continue to monitor the implementation of the policy and update it as the science around this disease develops.

26.26 Overall, we found that the Department has adopted a proactive approach to identifying risks that could threaten the health and safety of Canadians in the area of biologics.

The current regulatory framework for biologics is largely based on a traditional approach to regulations

26.27 The current regulatory framework for biologics is largely based on a traditional approach for developing

and maintaining regulations. Biological drugs, including vaccines, blood and blood products are subject to prescriptive regulations detailed in the *Food and Drugs Act* and several divisions of the Food and Drug Regulations. For years, as has been done in other countries, Health Canada has followed a traditional approach for regulating biological drugs and vaccines. This approach is well established and offers some benefits, particularly for products that require good manufacturing practices, on-site inspection and licence monitoring to ensure the safety and effectiveness of the products. However, the Department acknowledges that the Act and the Regulations have not kept pace with major advances in molecular biology and manufacturing technology. As such, the Department believes that this approach is not sufficiently flexible to deal with emerging products, such as xenografts, and other technological advances that characterize biologics.

26.28 Until recently, the Processing and Distribution of Semen for Assisted Conception Regulations (the Semen Regulations*)* represented the only regulatory framework in biologics that incorporated by reference in the Regulations standards developed by a third party. However, similar frameworks are planned for tissues and organs, xenografts, and blood and blood components, excluding fractionated blood products.

Health Canada is moving toward a standards-based regulatory approach for some biologics

26.29 The Semen Regulations were introduced in response to a recommendation of the 1993 Royal Commission on New Reproductive Technologies. In June 1996 they sought to establish minimum national standards that would decrease the risk of infectious disease transmission through semen when used in assisted conception. The Regulations made reference to specific sections of the Guidelines for Therapeutic Donor Insemination that had been developed and published by the Canadian Fertility and Andrology Society in 1988 and later revised in 1992. In effect, these guidelines (to the extent they were specifically referenced) were regarded as standards that had to be followed. The guidelines were largely voluntary until 1996.

26.30 In 1996 and 1997 the Department decided to develop similar frameworks for tissues and organs, xenografts, and blood and blood components (excluding fractionated blood products). The blood framework would contain compatible standards for hospital blood banks. Under this model, national standards of recognized standards development organizations would be referenced either in whole or in part in the Food and Drug Regulations. Requirements for registration or licencing of service providers, adverse event and activity reporting and compliance enforcement would be the subject of stakeholder consultations. These frameworks are expected to be in place by 2001–02 or earlier.

26.31 In recent years Health Canada has consciously moved toward adopting standards-based regulatory frameworks that reference the standards of standards development organizations for some biologics. The Department believes that these frameworks will give it greater flexibility to respond and adapt to rapid advances in technology and to the diverse nature and risks of biologics. However, the Department has concerns that the standards–based approach will not always keep pace with the expected rate of technological change. Only the standards development organizations can change their standards. For this reason, Health Canada may be unable to influence changes in the standards that it feels are necessary because divergent views may make consensus difficult — a basic principle of the model. This limitation

Health Canada has recognized that a variety of frameworks and approaches are necessary to deal with the wide spectrum of risks associated with biologics.

could significantly lengthen the process because the Department would have to initiate regulatory amendments if it decides that the changes are critical. As a result, Health Canada is considering the option of referencing internally its own technical standards, which it could change as necessary.

26.32 Depending on the nature and risks of a product and what is currently known about it, Health Canada can follow various approaches for regulating biologics. Different approaches have benefits and limitations. Because scientific knowledge is rarely complete, the Department must take into account the best available knowledge and weigh it against the possible outcomes when choosing an approach. Health Canada has recognized that a variety of frameworks and approaches are necessary to deal with the wide spectrum of risks associated with biologics. However, the Department has not developed criteria and guidelines to help its officials decide on what approach to adopt.

26.33 Health Canada should develop clear criteria to assist its officials in determining which regulatory approach is the most appropriate for a given situation.

Department's response: *Agree. In addition to the existing Treasury Board guidance concerning regulatory tools, a Legislative Instruments project has been undertaken to address the challenges presented by the unique situations relative to biologics.*

We found that Health Canada has had difficulty managing the workload of pre-market reviews of new biological products and conducting post-market assessments of products.

Implementing traditional prescriptive regulations presents challenges

26.34 Under their prescriptive regulations, biological drugs, including vaccines are subject to detailed pre-market reviews, including laboratory testing before their approval for sale in Canada. For all of these products, Health Canada validates manufacturing methods and conducts pre-approval inspections of facilities in Canada and abroad and inspections of the manufacturing processes and facilities in Canada following approval. These two types of inspection are designed to ensure that the manufacturer (or blood collection facility) and the products comply with detailed regulatory requirements, including good manufacturing practices. Where applicable following market authorization, the Department also tests the products and authorizes their release lot by lot to ensure their safety and efficacy.

26.35 This regulatory framework requires a complement of sufficiently trained staff and surveillance systems. We found that the Department has had difficulty managing the workload of pre-market reviews of new biological products and conducting post-market assessments of products. Because of these difficulties, there is a significant backlog of new biological drug submissions, established performance targets are often missed and post-market assessments are incomplete. These problems are expected to worsen with the implementation of proposed changes to the regulatory framework that will decrease the present 60-day default period for approval to only 30 days for many clinical trial submissions. The Department received the authority to increase staff to meet the demands of this shorter approval time. However, management has low expectations for finding qualified resources in the immediate future. It is estimated that this shorter default period will further increase the backlog of submissions for new biological drugs.

26.36 Adequacy of human resources. In November 1997 the Krever Commission recommended that the Bureau of Biologics and Radiopharmaceuticals be given sufficient resources to carry out its functions properly. In 1998 the government announced a new investment of $125 million over the next five years to strengthen Health Canada's blood safety program, including

regulatory and surveillance programs for related biologics. The Department also received permission to hire 84 full-time employees beginning in 1998–99 and up to a total of 133 by 2000–01.

26.37 According to an internal report, the Department had not filled by August 2000 30 of 94 positions allocated to the Therapeutic Products Programme for 1999–2000. Vacant positions were identified as "staffing in progress" or "staffing to be initiated" and pertained to compliance and enforcement investigations, pre-market and post-market reviews, post-market surveillance, regulatory research and policy development. The report attributed these shortfalls mostly to a lengthy staffing process and the unavailability of qualified candidates. Our interviews with departmental managers revealed additional reasons for being unable to staff these positions. These reasons include non-competitive salaries, management's inaction to initiate staffing due to a lack of time to hire and train new recruits and potential candidates' unwillingness to work in biologics in a post-Krever environment.

26.38 Post-market surveillance and ongoing risk assessments. Post-market surveillance allows for reporting to the Department of unforeseen adverse reactions and events. (These reactions and events are undesirable side effects experienced by patients, but not foreseen at the time the product was approved.) It also provides information to undertake ongoing risk assessments. To protect the health of Canadians, we would expect the Department to know quickly if any approved product has unexpected adverse effects. We would also expect the Department to systematically assess the risk and effectiveness of approved biological products.

26.39 While the established regulatory regime for biologics provides for post-market surveillance and ongoing risk assessments, we found a number of problems in these activities. There was little post-market surveillance of biological drugs supported by comprehensive data. The Bureau of Biologics and Radiopharmaceuticals often did not review and assess adverse reaction reports for products under clinical trials in a timely manner. Further, the Bureau of Licensed Product Assessments does not have a database to adequately process, analyze and disseminate information on adverse reactions and events for biologics. In addition, we have learned that the Department does not review adverse reaction reports from industry in other countries; it stores them in boxes. The Department attributes these problems largely to a lack of qualified candidates for vacant positions.

Health Canada had not filled by August 2000 30 of 94 positions allocated to the Therapeutic Products Programme for 1999–2000.

26.40 We also found a weakness in the reporting requirements for post-market surveillance. Even if the Department could adequately process and disseminate post-market assessments, its ability to assess risks is limited given that health practitioners' reporting of post-market events is voluntary. We recognize that Health Canada has no authority to compel physicians to report these events and that non-reporting is largely beyond its control because authority for medical practitioners rests with the provinces. However, the result of this weakness has been a long-standing concern for inadequate reporting. As such, the Department plans to more proactively obtain this information by contracting targeted studies as part of its strategy to strengthen its post-approval assessment activities.

26.41 Health Canada should take measures to ensure authorized positions are staffed.

Department's response: *Agree. Management recently approved a special Human Resources Initiative to accelerate recruitment. The project will focus internally on the retention of the highly qualified staff needed to deliver the program and externally on attracting and*

We found a number of problems in Health Canada's post-market surveillance activities.

recruiting highly specialized staff to fill the numerous vacancies in a timely fashion.

26.42 Health Canada should implement sufficient databases to adequately process, analyze and disseminate information on adverse reactions and events for biologics.

Department's response: *Agree. A partnership arrangement is being developed with the U.S. Food and Drug Administration for a combined database which will contain both U.S. and Canadian adverse event reports. Canadians will be better served by having access to a much larger database with information on rare, but critical, adverse reactions.*

Health Canada did not inspect or monitor the compliance of semen banks from the implementation of the Semen Regulations in June 1996 to March 1999.

Early experiences in using and referencing standards in regulations for biologics

26.43 The subsequent standards-based models planned for blood and blood components (excluding fractionated products), tissues and organs, and xenografts are different in some ways from the semen model. Yet the approaches and issues are sufficiently similar to gain valuable lessons that can be applied more broadly. We have noted the intended benefits of standards-based regulatory approaches over traditional regulatory approaches. These benefits include greater flexibility in changing regulations to ensure currency. Greater compliance is also expected because the regulations would be largely derived from consensus of all the interested parties. However, Health Canada's experience with the implementation of the Semen Regulations demonstrates that standards-based regimes can also present challenges for the regulatory authority. Some of these challenges, such as the lack of compliance verification, can be problematic, irrespective of the regulatory approach. Other challenges, such as the need to maintain transparency and flexibility when using third-party organizations, are specific to standards-based regimes.

Health Canada's experience demonstrates that standards-based regimes can present challenges for the regulatory authority.

26.44 Lack of compliance verification. Health Canada did not inspect or monitor the compliance of semen banks from the implementation of the Semen Regulations in June 1996 to March 1999. Although an accreditation process and inspection regime were intended to be part of the regulatory framework developed in 1996, these activities did not occur. Nor were there any plans established before 1999 for the inspection of semen processing facilities and standard operating procedures for inspection did not exist.

26.45 Reasons for not inspecting these facilities before March 1999 are unclear. Our interviews with Health Canada officials revealed various opinions on this inaction; however, we found no documented risk analysis to support it. The officials informed us that resources and attention were focussed on blood — the priority at the time. The risk of infectious disease transmission through semen was perceived to be low relative to blood. As well, the transmission of disease was considered unlikely because there had been no reported cases of sexually transmitted diseases through semen using assisted conception since the Regulations came into force in 1996. Adding to the lack of attention were the departure of key personnel and organizational changes, which affected the overall inspection strategy of the Department shortly after the introduction of the Regulations.

26.46 In March 1999 problems identified by an Ontario semen bank initiated that following summer a national investigative inspection by Health Canada of all known semen establishments. The Department found that 43 of the 51 establishments under investigation did not comply fully with the Regulations. Of these 43, 17 did not perform the required tests for specific infectious diseases, and more than half did not maintain sufficient records for Health Canada to determine

that they had done the required tests. As a result, the Department detained much of the semen supply for assisted conception in Canada, which created considerable anxiety among recipients.

26.47 Overall, we observed that the Department's semen investigation was comprehensive and it took action to mitigate risks. In April 1999 the Bureau of Compliance and Enforcement established an inspection program for all known semen establishments. The Bureau of Biologics and Radiopharmaceuticals performed health hazard evaluations to determine the extent of risk to public safety where non-compliance was observed. Shortly thereafter, the Bureau of Compliance and Enforcement began to formulate and test standard operating procedures for investigative inspections of semen establishments. In addition, the Department trained compliance officers to give them the knowledge and skills for inspecting these establishments.

26.48 The 1996 guidelines referenced in the Semen Regulations did not provide needed flexibility. These guidelines were developed by the Canadian Fertility and Andrology Society, a not-for-profit corporation. The members of the Society are volunteer practitioners and scientists involved in reproductive medicine and fertility research. Because the Society is not a national standards development organization, there was no specific responsibility for it to follow established procedures for reviewing and updating the guidelines. Health Canada also did not assume this responsibility, and no effort was made to periodically review and update the guidelines until 1999.

26.49 The guidelines were very specific about what tests were to be used for donors and semen to detect infectious diseases and when they were to be used. The semen investigation by Health Canada revealed significant technological advances in equivalent and sometimes more sensitive tests, which some banks were applying. The guidelines were inflexible because they did not allow for any tests other than those that were specified. Six of the investigated semen establishments had their semen supply detained because of non-compliance with the Regulations' mandated tests. Ironically, the one case of sexually transmitted disease, which was identified in the investigation, does not appear to have been the result of non-compliance with the guidelines. The semen establishment had done the test mandated by the guidelines. However, this test has since been proven to be less effective in detecting the disease than the newly developed test. While this case is still under investigation, the current guidelines have been updated to include the newly developed and more sensitive test.

Later in 1999 Health Canada found that 43 of the 51 establishments under investigation did not fully comply with the Semen Regulations.

26.50 The guidelines were revised by the Canadian Fertility and Andrology Society in consultation with Health Canada following the semen investigation. Introduced in March 2000, they too were acknowledged by departmental officials as being very prescriptive and not allowing for alternate tests. Recently, however, Health Canada changed the Semen Regulations to authorize alternate tests, which it must approve, in order to achieve the flexibility that standards-based regulatory frameworks are intended to provide.

26.51 Efforts to maintain transparency and flexibility. The introduction of standards-based regulatory frameworks has presented a new element about which regulatory authorities need to be concerned. The involvement of the standards development organizations in the frameworks means that the organizations could be susceptible to litigation if something goes wrong. The Semen Regulations until recently made specific reference to guidelines of the Canadian Fertility and Andrology Society. The Society stated that its March 2000 guidelines would be withdrawn on 1 August 2000. Departmental officials

The involvement of standards development organizations in standards-based frameworks means that the organizations could be susceptible to litigation if something goes wrong.

informed us that the Society had concerns about legal liability. The withdrawal of the guidelines would have created a void in the regulatory framework for donor screening and semen testing for infectious disease agents as of that date. However, Health Canada incorporated on 27 July 2000 specific sections of the guidelines into a departmental directive, which is now referenced in the Regulations.

26.52 The Department faced two challenges in referencing standards contained within its own directive. It had to ensure transparency of decision making when amending the guidelines in the directive. At the same time, it needed to maintain flexibility for making changes quickly to keep pace with technological advances.

There have been numerous delays in establishing national safety standards for the transplantation of human tissues and organs.

26.53 Federal regulatory policy requires that the regulatory authority ensure public scrutiny when changing the regulations as part of the prescribed process. By doing so, the authority ensures the transparency of decision making and ultimately accountability. Accredited standards development organizations must consult stakeholders and obtain a consensus before it can change its standards. The organizations, by their independence, ensure that the authority does not have a mechanism to circumvent public scrutiny of the regulatory process, which helps to ensure public accountability. If a department references its own internal directive in the regulations, it creates a process that does not require public consultation when it changes the directive.

26.54 Health Canada wanted to ensure that the public could provide input on future changes to the standards for semen for assisted conception, which are in the internal directive. Therefore, the Department used a static reference (i.e., changes cannot be made without going through the prescribed regulatory process) to allow the public to do so. This decision was in lieu of the ambulatory reference, which allows for amendments from time to time. However, the Semen Regulations have now lost the primary advantage of the standards-based approach, i.e., providing the flexibility to make changes quickly in order to keep pace with technological advances. Health Canada intends to address this problem in the new regulatory framework for tissues and organs, including reproductive tissues, which is under development.

26.55 As part of the regulatory framework for tissues and organs, the Department is developing standards for tissues and organs that are separate from standards for semen for assisted conception. As was the case with semen, the standards development organization involved in the regulatory framework for tissues and organs was also concerned that it might be susceptible to future litigation. This organization requested legal indemnity beyond an amount which it could bear in the event of legal action over the standards. The federal government agreed to indemnify the organization by accepting to pay any possible claims that court decisions would impose beyond this amount. Once the contract has been finalized, it is expected that the standards development organization will continue to maintain the standards for tissues and organs and maintain transparency and flexibility of the proposed regulatory framework.

26.56 Delays in the development of a regulatory framework for tissues and organs. Like several other countries, Canada is developing a regulatory framework for tissues and organs. However, it has been doing so for a number of years, and there have been numerous delays in establishing national safety standards. In October 1995 Health Canada hosted the National Consensus Conference on the Safety of Organs and Tissues Used in Transplantation. Following the conference, a working group of transplant practitioners drafted a Canadian general standard for the safety

of organs and tissues used in transplantation.

26.57 In its April 1999 report, the Standing Committee on Health saw a clear role for the federal government in developing regulatory standards for the safety and quality of organs and tissues, similar to those for blood and semen. It also noted that formalizing the Canadian general standard for the safety of organs and tissues used in transplantation had taken several years. There have been frequent calls for strong national safety standards. For this reason, the committee recommended that the Minister of Health have the standard and its subsets approved and made mandatory as soon as possible, preferably within six months, through incorporation by reference into regulations under the *Food and Drugs Act*. The Department expects to complete a regulatory framework for tissues and organs in 2001–02.

26.58 Health Canada is proactive in planning a regulatory framework for xenografts. Organ and tissue transplants have been taking place in hospitals for a number of years. Xenotransplantation, though not scientifically perfected, is rapidly evolving, and some investigational studies have been proposed. However, it is generally accepted that the potential benefits of this medical technology do not come without risks to the transplant recipient and the general public.

26.59 In 1997 Health Canada sponsored a national forum on xenotransplantation. The forum recommended that the Department develop a standards-based regulatory approach for xenografts. It also identified other issues such as patient ethics that need to be addressed.

26.60 In its April 1999 report, the Standing Committee on Health recommended that Health Canada be proactive in informing and consulting the public on xenotransplantation. Further, the Department would need to ensure that clinical trials for xenografts not be approved until the proposed xenotransplantation standards are enforceable.

26.61 Currently, there are no clinical trials of xenotransplantation that have been approved in Canada. We noted earlier the mandate of the Expert Advisory Committee on Xenograft Regulations. In September 1999 Health Canada published a proposed standard for xenotransplantation as an eventual criterion for clinical trials and regulations for xenotransplantation in Canada. The Department expects to complete a regulatory framework for xenografts following public consultations in 2001.

Health Canada is proactive in planning a regulatory framework for xenografts.

26.62 Lessons learned from implementing standards-based regulatory frameworks. Based on its use of referenced standards in the Semen Regulations, the Department is studying lessons learned from implementing standards-based regulatory frameworks. The objective of the study is twofold: to assess the outcome of the Therapeutic Products Programme's experience with incorporating referenced standards into regulations; and to identify positive and negative after-effects, areas for improvement and issues on the use of such frameworks for other biologics. At the time of our audit, the Department had not completed the study or presented it to senior management for review.

Based on its use of referenced standards in the Semen Regulations, Health Canada is studying lessons learned from implementing standards-based regulatory frameworks.

26.63 In our opinion, this study is an important undertaking by the Department. We are encouraged that it reflects many of our observations on the implementation of the Semen Regulations. In particular, the study reveals the need that standards be relevant and flexible in order to keep pace with technological advances, that compliance be verified and that accountability be assured for regulations referencing technical standards of the Department. Resolving these issues now is especially important given Health Canada's plans to implement standards-based regulatory frameworks for blood and blood components (excluding

fractionated products), tissues and organs, and xenografts.

26.64 Health Canada should complete its case study pertaining to the lessons learned in using standards-based regulatory frameworks, which draws upon the experience of implementing the Semen Regulations.

Department's response: *Agree. The case study pertaining to the lessons learned is being finalized, prior to presentation to senior management for review, but the principles of lessons learned are already being applied.*

26.65 Lessons learned from implementing the Semen Regulations should be applied to future standards–based regulatory regimes, as appropriate.

Department's response: *Agree. The case study of lessons learned from implementing the Semen Regulations, along with the policy paper from the Legislative Instruments project will be integral to the application of future standards–based regulatory regimes, as applicable.*

In recent years there have been several reviews and evaluations applicable to biologics. They identified needed improvements that affect biologics. Our audit has raised many of the same concerns.

Evaluation and Ongoing Review

Many of the reviews point to problems observed during our audit

26.66 We expected Health Canada to undertake periodic evaluations or other reviews that measure program effectiveness and to report their results. We also expected the Department to have in place a system that continuously measures performance and to report on its performance.

26.67 As in any regulatory program, the regulatory authority is primarily responsible for ensuring the effectiveness of its regulations and established standards. Irrespective of the regulatory approach it adopts, the authority's periodic evaluations (or other reviews) and ongoing performance measurement are essential to assess the effectiveness of the regulations and the approach. These functions are especially important given the impact of biologics on the health and safety of Canadians; the rapidly changing environment that characterizes biologics; and the Department's move to adopt standards-based regimes for other biologics.

26.68 In recent years there have been several reviews and evaluations applicable to biologics, including the 1997 final report of the Krever Commission of Inquiry on the Blood System in Canada, various reviews of the drug approval process, and the evaluation of the cost recovery initiative completed this year. Although some of these reviews and evaluations were not specific to the regulation of biologics, they, nonetheless, identified needed improvements that affect biologics.

26.69 Among other things, the Krever Commission made recommendations to strengthen the regulation of biologics, including the need for adequate resources. Other reviews also identified concerns about allocating adequate resources, not meeting performance targets, and making decisions open and transparent. Our audit has raised many of the same concerns.

26.70 The Department monitors its performance against the Krever Commission's recommendations that apply directly to Health Canada's sphere of operations. The Web site of the National Blood Safety Council contains information on the status of Health Canada's and others' implementation of the Commission's recommendations. There are performance reports on quarterly and annual biological drug review submissions, which list established targets for approving these submissions. The Department measures its performance against these targets. However, we did not find performance targets for monitoring other activities, such as the completeness

and timeliness of adverse reaction and event reporting.

26.71 The Department is developing an evaluation framework for its blood safety program. However, its most recent evaluation plan does not cover other biologics. The Department also intends to conduct an expert review of all activities related to blood regulation and surveillance by November 2002. This review is in response to the Krever Commission's recommendation that the Bureau of Biologics and Radiopharmaceuticals be audited every five years.

26.72 We encourage the Department to continue these activities given the importance of biologics and the safety considerations that we discuss in this chapter.

Organizational Realignment

A product life–cycle approach to managing biologics is being examined

26.73 In April 2000 Health Canada announced a realignment of its activities, partly to strengthen its health protection capabilities. Among other things, it has proposed the creation of a new directorate of biologics and genetics.

26.74 The management of biologics depends greatly on specialized expertise. The components of each biological product have varying characteristics that require specialized safety considerations. The Department is examining an approach to managing biologics based on products' life cycle. The approach would build product knowledge continuity, from the time a biological product is presented for pre-market review to the time it is taken off the market. To achieve this approach, one consideration is to gather Health Canada's experts in biologics and use the same team of pre- and post-market reviewers to monitor adverse reaction reports.

26.75 The Department's discussions on organizational realignment will address the issues identified in our audit and other reviews, including the following:

- staffing key positions that are still vacant;
- implementing sufficient databases to adequately process, analyze and disseminate adverse reactions and events;
- verifying compliance with regulations;
- ensuring the periodic review and update of referenced standards; and
- addressing the issue on referencing in regulations the Department's own technical standards.

26.76 Accordingly, the Department plans to adopt next year a cautious and measured approach to establishing a new organizational structure for regulating biologics.

Conclusion

26.77 Health Canada is taking a reasonable approach in developing and implementing frameworks and approaches for regulating different biological products. However, the Department faces some important challenges. It needs to establish more formal guidance to determine which regulatory approach is most appropriate for a given situation. It also needs to maintain the currency of regulations and have sufficient qualified staff to deal with the rapid technological advances in biologics.

26.78 Health Canada has adopted new regulatory approaches so that it has greater flexibility to meet these challenges. However, the Department is concerned that even these new approaches may not be able to keep pace with the expected rate of technological change.

26.79 The Department follows a traditional approach with prescriptive regulations to regulate most biologics.

This framework is well-established and offers some benefits. However, Health Canada believes it is not sufficiently flexible to deal with emerging products and other technological advances in biologics.

26.80 The Department is moving toward a standards-based regulatory approach for some biologics. However, this approach also has its unique challenges. The Department needs to ensure that the standards on which its regulations are based are up-to-date and provide the needed flexibility to respond to new knowledge or technological advances. In addition, Health Canada needs to address the accountability issues that have emerged as a result of standards writing organizations' concerns for legal liability. Overall, it needs to apply the lessons learned from implementing the Semen Regulations in the development of standards-based regulatory frameworks planned for other biologics.

26.81 The government is accountable for all of its regulations, regardless of how they are developed and how standards are incorporated or referenced in regulations. The government is also accountable for implementing the regulatory regime and establishing adequate compliance and enforcement systems. As well, continuous review and evaluation by Health Canada are essential to assess the effectiveness of its regulations and approaches used.

26.82 Rapid advances in science have resulted in increasing regulatory challenges. Many of the federal laws that govern health and safety were developed decades ago. Today, science is yielding new products that up until recently were unimaginable. Some products and practices carry potential health risks and raise difficult questions that current legislation may not be fully equipped to address. This trend is expected to continue at an increased pace.

26.83 It is important that regulations remain current. It is also necessary to ensure that the tools required to put in place regulations — or other interventions — are also current and sufficiently flexible to deal with changing demands.

About the Audit

Objective

We set out to determine how well Health Canada's regulatory regime is working in the regulation of biologics.

Scope and Approach

We examined Health Canada's framework and approach for regulating biologics. We looked at its process for deciding where regulations or standards are required for certain biologics. We also looked at the various frameworks and processes for providing the Department with information on the effectiveness of adopted regulations and approaches. We focussed on the management of the regime for regulating biologics. Therefore, we did not conclude on the effectiveness of specific regulations or on the safety of specific products.

Criteria

Regulatory programs are to be designed, organized and implemented based on the following:

- a proactive anticipatory approach, where appropriate;
- a comprehensive analysis and assessment of the nature and magnitude of risks;
- a comprehensive analysis of alternative regulatory approaches and tools to address identified risks;
- a clear understanding of the respective roles and responsibilities of different levels of government, industry and other parties to facilitate collaboration and enforcement in protecting public health and safety;
- prescribed standards, where appropriate and applicable;
- up-to-date legislation and regulations, where required;
- timely, efficient and effective implementation of regulatory action, including, where appropriate, conformity and compliance with prescribed standards, compliance with activity reporting and adverse events reporting, and inspections and responses to incidents of non-compliance or serious adverse events;
- a sound national database, where appropriate; and
- continuous review and appropriate accountability structures, including procedures to measure the effectiveness of regulatory program activities and to report results.

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