INTERVIEW

In an exclusive interview with *Regulatory Rapporteur*, **CELIA LOURENCO**, *Director General, Biologic and Radiopharmaceutical Drugs Directorate*, and **DR J PATRICK STEWART**, *Director General, Therapeutic Products Directorate*, both at Health Canada, talk about how the agency ensures the safety of pharmaceutical and health products

Regulating healthcare products in Canada

BY AMAN KHERA,
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Q: Could you tell our readers a bit about your background, what attracted you to the regulatory arena, and how you came to join Health Canada?

Celia Lourenco (CL): I completed a PhD in pharmacology and always had an interest in the area of drug development, and joined a lab doing my PhD studies that was involved in developing radioactive molecules. That really drove me into the area of drug development. At one point I noticed there was a post-doctoral fellowship opportunity at Health Canada, and I decided to apply, and the rest is history.

J. Patrick Stewart (JPS): I also started out with a science background. My initial training was in geology, I did a geochemistry degree and then did a master's degree at University of Toronto in geology. Around the time I finished my master's degree, I was working in base metal exploration and the world base metal crisis resulted in a downturn, so employment opportunities weren't good, so I went back to school and did a medical degree. Subsequent to that, I did a residency in family medicine and emergency medicine and worked for 14 years in a tertiary care hospital, an emergency department in Ottawa. I spoke to a colleague who had moved over to Health Canada, and found it interesting, so I explored that opportunity and was hired as a medical officer in the Medical Devices Bureau 15 years ago.

Q: What does your current role involve, and what do you consider your favourite aspects of this role?

CL: I'm the Director General of the Biologic and Radiopharmaceutical Drugs Directorate, responsible for reviewing both clinical trials and authorising clinical trials, as well as market approval for biologics and radiopharmaceuticals, so I have a lot of responsibility. I get to work with incredibly smart people, scientists and experts, which is very intellectually stimulating. We're always learning about new therapies, and the science of drug development continues to change. I really enjoy contributing to ensuring Canadians receive drugs that are safe, effective and of high quality. I enjoy working with a variety of stakeholders, so not just my colleagues like Pat within the branch, but outside with a number of different stakeholders, within the government and outside the government, across all the sectors, including the healthcare system partners and industry stakeholders. We're all in this together with the ultimate goal of safe and effective drugs for Canadians.

JPS: I'm the Director General of the Therapeutic Products Directorate (TPD). It's one of the directorates in the health product and food branch, and we are responsible for prescription drugs and regulating drugs for human use. Before authorising the drugs, we verify that they meet safety, efficacy and quality requirements of the Food and Drug Act. We also approve clinical trials for therapeutic pharmaceuticals and look after the special access programme. I am part of a team of about 450 people, and I feel privileged to be in the role I am in and work with great colleagues like Celia at the branch level of the executive committee. It's an interesting job that is never dull. There are always new aspects and challenges. We're always looking for ways to become more helpful and stay relevant. What I find the most interesting is how things evolve and how we actually play a vital role, but we need to stay flexible at the same time, too, to stay relevant.

Q: What changes have you introduced within Health Canada at your directorates since you took on the role, and what are your aims for future changes within the organisation?

CL: I joined the directorate almost two years ago. I found it to be a solid, well-established and well-run organisation. It has met all its performance standards for what we call cost-recovered submissions, as well as non-cost-recorered submissions (ie, those for which industry pays fees versus those that it doesn't). We really have a fantastic team that is dedicated and ensures that we meet those performance standards, and makes sure we get drugs reviewed and approved on time. I did implement some realignments and a name change of the directorate, just to make it more precise about the products that we regulate, but the major functions of the directorate have been maintained. I do expect the directorate to evolve in the future as we expect new cutting-edge therapies to emerge, such as gene and cell therapy. That will certainly challenge us to adapt and be agile in how we will regulate in the future. I'm looking forward to that challenge.

JPS: Similar to Celia, the directorate I work in is staffed by an enormous amount of qualified, dedicated people, and, if I was to say I introduced any change within Health Canada, it's only to say that I contributed to the change because everybody is rowing in the same direction and we're working together. In the role of

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Director General, you do have the ability to influence the focus, scope and effectiveness of these projects. I grew up in the TPD, the Medical Devices Bureau was there and I was leading the Office of Clinical Trials for a period; I was supporting the Director General and Director General's Office for a while, and I had a stint being the Director General of the Marketed Health Products Directorate (MHPD) and then, for the past three years, I've been back leading the TPD.

I've been involved in modernisation projects for the review of drugs and devices. TPD was leading seven of the 15 projects and I played a role in making sure that those advanced and had appropriate focus and were delivered. Just before the COVID-19 pandemic, we were moving into a regulatory modernisation project that the whole branch was embraced in and we've been driving some of those projects out of the TPD. I've been contributing to those projects. We as a branch also have focused a lot on our stakeholders, both within the department, as well as within the healthcare system, and also internationally.

I've had an opportunity to be involved in international organisations and built relationships and we are continuing to build stronger relationships. We also have an increasingly intertwined relationship with the European Medicines Agency (EMA) and of course the US FDA is always an organisation that we enjoy dialogue with. Going into the future, I hope that the TPD and our branch can continue to evolve. Regulatory change is not a quick process, it requires proper procedure and protocol and we try to think ahead of the game so that we can put in place changes that will support the evolution of how drugs are being developed, how the industry is functioning, and how the healthcare systems are evolving.

Q: Do you think Health Canada has been affected by the increasing requirement for global transparency in regulatory processes?

CL: Transparency has been one of our strategic priorities over the past several years. It did require a culture change. A decade ago, perhaps, we were "closed" by default, meaning that everything was confidential. Now transparency is the default in everything we do. We have implemented several transparency measures over the past several years. We have several initiatives, like our summary basis of decision document, which summarises the regulatory decision when a new drug is approved. We have shortened versions which we call regulatory decision summaries,

which provide a quick two-page summary of the decision on a drug approval, whether it's a new drug or a change to an existing drug.

We also have numerous databases. We have a clinical trials database that lists all clinical trials we have authorised. We have a drug product database that lists information about the products we have authorised in terms of the instructions for use and side effects associated with the drug. In April last year we launched the "Public Release of Clinical Information" initiative, which aims to provide information to healthcare providers as well as scientists, academics, and Canadians in general about the clinical safety and efficacy data that were used in the decision process, ie, the results of the clinical trials that were conducted to support the approval of the drug.

JPS: One other aspect is in the post-market space. We do a lot of safety reviews of drugs, and then may make decisions to change labelling or not. Up until about eight years ago we weren't very transparent about that, but we now also put out summary safety reviews that explain the process and rationale for our decisions and conclusions. If requested and required, we could also release the full review report.

The other thing we've evolved is our product monograph, the document that explains the information that was submitted about the product, the prescribing information and we've evolved the part 3 of that, which is for patients. We're trying to adapt that into more of an electronic format; our long-term vision is to have this available to pharmacists so they can easily access Canadian-specific information for patients about a product. We would also like Canadians to have access to our health product registry. We're trying to produce as much of the information available about the products we regulate in a user-friendly format and trying to make the language plain and understandable.

> **We've been able to continue to meet the performance standards despite the COVID-19 pandemic and have been expediting all of our COVID-19 clinical trials**

Q: What is the average length of time it takes Health Canada to assess and approve applications, variations and renewals? What is the percentage of approvals being achieved within a timeframe?

JPS: We publish our annual report (available on our website) and the Centre for Innovation Regulatory Science (CIRS) produces a comparative report of different regulators. We have our various targets, we have priority review, expedited review, and standard review. We have our performance targets for our clinical trial applications and we have performance commitments. We have just introduced a new framework for cost recovery where we've had to meet our average performance time. Up until this year for every submission that we go beyond the cost recovery performance target, there is a penalty applied, so our challenge is to try to approve every submission and make a regulatory decision within the cost recovery target. So far we're meeting our cost recovery targets. There's been a global shift to an increasing number of submissions being done as either priority or an expedited review. The FDA is leading that with the number of submissions in the past couple of years that follow expedited timelines.

With COVID-19-related clinical trial submissions, our default time is 30 days. We've been able to assess all COVID-19 trials in a much shorter time, some initially within a day or two. We've had one COVID-19 related drug submission, for remdesivir, and again, we were able to achieve the review in a six-week timeframe instead of the 180- or 220-day performance target.

Q: Do you have any generic substitution or reference pricing?

CL: From the biosimilars perspective, the pathway for market access is different from generics. It's not the same abbreviated new drug submission pathway but a regular new drug submission, with the data comparing the biosimilar to the innovator. We don't issue a declaration of bioequivalence. We review the application and issue an authorisation based on the data submitted and the drug then enters the market as a biosimilar. It's then up to the provinces to determine whether it is interchangeable or not, or whether it can be substituted. From our perspective, the review process confirms that we do not expect any meaningful clinical differences on efficacy and safety between the biosimilar and its comparator.

JPS: Under the Food and Drug Act, we do have an abbreviated new drug submission pathway where generic companies using bioequivalence studies on the Canadian reference product obtain a drug approval as an equivalent to an innovator product. They're then able to go to the various purchasing organisations within the provinces to get a declaration of equivalence and get generic substitution. All of the dealings beyond issuing an approval based on an assessment of the evidence provided, the pricing, whether it's deemed to be equivalent and the timelines of all that are done by the provincial bodies.

Q: Does Health Canada conduct health technology assessments or is there a separate body that carries out the economic assessment of medicinal products?

JPS: Yes, there are separate health technology assessment (HTA) bodies: the Canadian Agency for Drugs and Technologies in Health (CADTH) and INESSS (Institut national d'excellence en santé et services sociaux). The CADTH undertakes the HTA for drugs and some devices for all the provinces except Quebec, and INESSS undertakes it for Quebec.

Previously, for a drug or device submission, once the review of the safety, quality, and efficacy was completed, the notice of compliance (NOC) would be issued and then an HTA would begin. We started an initiative working with the CADTH and INESSS to move that up so that the HTA would start six months before a NOC issuance was suspected. We were able to develop that process, it was piloted and now, somewhere around 50% of the innovator submissions that are coming in the past year have taken advantage of this alignment process. One other aspect of that project was to try to put in place a joint early advice – ie, the HTA body and Health Canada would provide sponsors with earlier advice in the drug development planning. This will help sponsors

Regulation during COVID-19

Has the COVID-19 pandemic had any impact on your agency's operational activities?

CL: Definitely there have been impacts. Essentially most of my staff and my directorate of about 370 employees are working from home. I do have some staff working in the laboratories – those who are responsible for our lot release testing for biologics such as vaccines and staff in our laboratory research programme. But most of the other staff are working from home. We have some staff who are parents of small children and it has been challenging for them, but they have been able to adapt and continue to contribute to their role, which is incredible. We've been able to continue to meet the performance standards despite the COVID-19 pandemic and have been expediting all of our COVID-19 clinical trials. We've been able to continue to review the other regular clinical trials as well as drug submissions. We continue to hold meetings with sponsors and provide advice to stakeholders, but that's all shifted to virtual meetings. For the most part it's worked well, sometimes there are connection issues, but we've been able to work through those. We're currently focused on ensuring we support the country's response to the pandemic from a regulatory perspective. We have taken measures to implement flexibilities, to facilitate clinical trials and to support our stakeholders at this unprecedented time.

JPS: It was a huge shift that we did quickly and successfully from working in the office to working at home. Some IT challenges were sorted out quickly. There was some flexibility afforded around hours of work and so forth and our staff are very resilient. Despite all these challenges we've been able to maintain our regular cost recovery performance targets, as well as expedite clinical trial reviews, as Celia has mentioned.

We've also been engaging more with other areas of the department and the government; other departments because of the need to call on expertise, and across the government because we needed to understand each other, how industry, science and economic development worked, how the public health agency was working, how we were working, and how our regulatory operation and enforcement branch was working.

We've been involved in a lot more meetings where we're sharing our expertise and coming to share information on some of the decisions we've had to make. As Celia mentioned, we've offered regulatory flexibilities and put in place interim orders for the medical device authorisations. There was a lot of flexibility around hand sanitisers. We've put in place a clinical trial interim order and the regulatory operations enforcement branch put in interim orders around flexibilities with drug shortages. We have to look at the potential products coming in from a quality point of view have been supporting the regulatory operations branch. We continue to look at ways that we might advance other interim options to help.

Also, there has been a fair bit of engagement with the International Coalition of Medicines Regulatory Authorities, watching the COVID-19 clinical trials that are ongoing and trying to share as quickly as possible any results that are coming up. We've leveraged our relationships globally to commit to share information between regulators.

have a better sense of what the regulator and what the HTA assessor are looking for from endpoints to support decisions.

It is important to note that the agencies do work independently. Both the CADTH and INESSS have some similarities but their decisions are independent. Of course, their decisions are independent from Health Canada's decision. Health Canada is about the benefit–risk of a drug, whereas the health technology agencies look at cost–benefit.

Q: What is Health Canada's strategy to combat the distribution of falsified, counterfeit medicines?

JPS: It is a very challenging area. There are two aspects to this. You've mentioned falsified and counterfeit medicine. There's also falsified or misleading advertising around products. In our branch the Marketed Health Products Directorate (MHPD), in collaboration with the regulatory operation and enforcement branch, do have a programme to monitor advertising and promotion. There are clear statutes in our regulations around what can be said or not said about health products and their claims. This is monitored and they deal with misleading advertising. In the context of COVID-19, they've been more proactive in looking at unfounded claims and taking action. Regarding actual importation and distribution, there is a joint monitoring programme with the Canadian Border Services.

Q: What are some important updates to Health Canada legislation readers should be aware of?

CL: We implemented legislation last year to embark on a regulatory renewal initiative, which we refer to as our Agile Regulations Project. The intent is to renew the current framework to eliminate outdated regulations and make it more risk-based and agile to respond to emerging technologies. We will be consulting with stakeholders in the coming months to move the project forward.

As part of that initiative we're also implementing a new advanced therapeutic products pathway, which will introduce a tailored approach to regulating innovative products that don't fit within the current regulatory framework. An example may be products such as 3D bio-printed tissues and 3D bio-printing of organs. Those may have characteristics that would fit, for example, our biologics framework, and other characteristics that would better fit under our medical devices framework. The objective is to tailor the requirements to ensure that the safety, efficacy, and quality of those innovative products will be appropriately managed and appropriately regulated. We will learn from the process and eventually determine whether such products can be transitioned into an existing regulatory pathway or a new pathway in the future. Products could also exit the market altogether if there are safety, quality or efficacy concerns.

We're also developing this particular advanced therapeutic products pathway to address those emerging challenging but interesting products, including gene therapies or cell therapy products that are individualised.

Q: How does Health Canada work with the EMA and the FDA?

CL: We work with the EMA and FDA on a multi-lateral level, such as through the International Coalition of Medicines Regulatory Authorities (ICMRA), International Council for Harmonisation, International Pharmaceutical Regulators Program and the

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Pharmaceutical Inspection Co-operation Scheme. Those are also opportunities for us to engage with the EMA and FDA experts to share information and knowledge. We've actively engaged with these agencies on COVID-19 as well for the past several months, both within the context of ICMRA as well as outside of that forum. Exchanging information with them has really been helpful, such as approaches to vaccines for COVID-19. These are key relationships and we nurture and value them.

JPS: We value both these relationships strongly. We have reached out and engaged at many levels, both from the heads of agency down to operational levels and we find these relationships valuable. With the EMA, we have been permitted to participate in some of its committees and we engage in cluster meetings. All these various touchpoints are extremely valuable for us to discuss common files and aligning to a possible degree. We have established confidential agreements that enable us to share information which otherwise couldn't be shared.

Q: What have been your agency's successes to date and what have you been most proud of?

CL: We're proud of our quality management systems. We're ISO-certified, both in our regular operation as well as our laboratories. We also pride ourselves in conducting reviews with scientific rigour and discipline, ensuring that only products that meet those internationally recognised standards will enter the Canadian market.

JPS: I'm proud of our reputation globally. We're not the size of, say, the FDA, but we're at the table with leading global regulators like the FDA, the EMA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). Our teams and specialists are sought for input and we influence global decision making so, from the point of view of Canadians, they can have confidence that the skill sets and the type of work we're doing is aligned with what other major regulators are doing.

Q: What do you anticipate being the highlights of Health Canada during the next 12 months? What do you think will be the most important issues the agency will face in the future?

CL: We hope that over the next 12 months we can make very significant progress in bringing high quality and effective products to market to address COVID-19 because this pandemic isn't going away any time soon. We also plan to move forward with the agile regulations and the advanced therapeutic products project. We also want to continue to engage internationally with our international partners through our Australia, Canada, Singapore, and Switzerland (ACSS) consortium. We want to evolve the work-sharing activities. It's very active and successful and we expect it to become part of normal business. We also want to continue to collaborate with other partners like the FDA, with which we are conducting parallel reviews in the oncology space.

JPS: We'll continue to evaluate non-COVID-19 therapeutics. There's still a vast number of clinical trials, special access programme requests and market authorisation requests coming in. We'll continue to strive to maintain our high standards for review of these and meet our performance targets.

Q: What do you see as the biggest challenge facing Health Canada in the next five years? What are your key objectives?

JPS: There are many challenges, but if I had to pick out a few it'd be the pace of change in scientific development, in manufacturing, and the design and modelling of trials. There is the evolution of what endpoints are relevant to Canadians with the use of real-world evidence and artificial intelligence modelling and to follow the changes in healthcare.

Globalisation is another big one, I think the drug shortage issues that have been happening over the past few years are partly because of globalisation and the lack of redundancy in the supply chain, but also globalisation in research and development. It's a competitive market to entice clinical trials and research and development in any domestic market based on global decisions around whatever factors they're considering. Because of all these factors we need to keep adapting our regulations to serve Canadians well, and to keep Canada on the radar as a country where global companies want to do research and development and where companies want to market their products. It is a competitive world out there and Canada only represents about 2% of the global sales market. We find that challenge is – in order to be able to be relevant and to be an effective regulator – we need to have the right skill sets. To evaluate these novel therapies to leverage advances in, for example, analytics and modelling, we may have to change some of the skill sets we are hiring for, so that we have people with slightly different backgrounds. And to adjust to these challenges and to stay relevant, we need to continue to enhance our international collaboration and work-sharing initiatives.

CL: In order for us to remain relevant as a regulatory agency and be able to be agile and respond quickly to innovative technologies as they evolve, we need to engage much more with the healthcare system, and with the innovators themselves to understand the technologies and to make sure we develop the right regulatory requirements that don't stifle innovation. And then, a follow-through right from the regulatory process all the way down to when the patient receives the treatment.

Added to that as well is the patient voice. Until recently, we have not necessarily engaged patients systematically such as how the FDA does. We need more patient engagement feeding into our regulatory processes and decision-making on challenging areas of regulation like orphan drugs and personalised medicines that may come through the advanced therapeutics pathway. ■