

Expert Analysis

## Stem Cell Therapy Regulation In Canada: Implications Of the Prochymal Approval

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On May 17, 2012, Health Canada issued marketing approval for Prochymal, a stem cell therapy used to treat children with acute Graft versus Host Disease (aGvHD). The development was heralded as the first stem cell product approved by regulatory authorities in the world.<sup>1</sup>

In this case, Health Canada outpaced the USFDA, which is still requesting further clinical data from the manufacturer, Osiris Therapeutics Inc.

### BACKGROUND OF THE PROCHYMAL APPROVAL

The Health Canada Report of the Expert Advisory Panel on Prochymal provides the context and rationale into why this particular stem cell drug was approved.<sup>2</sup> First, the drug targets aGvHD, which is a debilitating condition whereby the foreign immune cells from a bone marrow transplant attack the tissues of a transplant recipient.

In 50 percent of aGvHD pediatric cases, children do not respond to traditional systemic corticosteroid therapy (“refractory aGvHD”).<sup>3</sup> For up to 85 percent of these children, the condition can result in a slow and painful death.<sup>4</sup> This potentially tragic outcome led the panel to state that aGvHD “is such a devastating illness that the risk-benefit ratio would be acceptable even with the current efficacy data.”<sup>5</sup> Furthermore, aGvHD is a rare disease affecting a small patient population, which makes it difficult to obtain sufficient clinical data to verify the drug’s effectiveness.

Regulatory approval allows more patients to access the drug and therefore facilitates the collection of unbiased and longer-term data. Finally, preliminary trials satisfied the short-term safety requirements set out by Health Canada. Given these pressing issues and the risk/benefit analysis, Health Canada approved the drug via a Notice of Compliance with Conditions (NOC/c), which subjects Osiris Therapeutics to heightened post-market surveillance.

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The NOC/c process allows Health Canada to approve promising drugs for serious diseases that have no alternative treatments or where the alternatives present inferior benefit/risk profiles. An NOC/c decision subjects the product to heightened post-market surveillance by way of additional clinical trials and regular reporting to Health Canada.

Once the conditions are met and the clinical effectiveness of the drug is confirmed, the product will continue to have market authorization with conditions removed (*i.e.*, a Notice of Compliance without Conditions).<sup>6</sup>

The Panel recommended 15 years' follow-up of treated patients or follow-up until age 30, whichever comes first. This monitoring will focus on the development of tumours, infection and the presence of Prochymal in autopsies or biopsies.

In addition to long-term monitoring, the NOC/c requirements restrict treatment to children with refractory aGvHD and restrict access of Prochymal to physicians who have experience treating aGvHD patients.

#### **HEALTH CANADA: LEADERSHIP OR FLUKE?**

In contrast to Canada, the U.S. Food and Drug Administration authorized Prochymal for use in its Expanded Access Program, which allows patients to access life-saving drugs before market approval. However, special arrangements must be made by the patient's doctor to obtain the drug from the manufacturer when the drug has not been declared safe or effective.

The advantages to the Canadian pathway include the following:

- Prochymal has marketing approval in Canada (even though the approval is with conditions). This allows the manufacturer to market the drug to healthcare practitioners (in the United States, there would be restrictions on promoting Prochymal before it is approved).
- Health Canada was forced to either approve the drug with conditions or reject the approval (in contrast, in the United States, manufacturers have the option of seeking orphan drug approval, but the manufacturer must apply for orphan product designation before seeking marketing approval, thereby extending the regulatory approval process).
- Health Canada was willing to examine efficacy in a subset of the patient group.<sup>7</sup>

These differences in process allowed Health Canada to beat the FDA in approving Prochymal. Despite the belief that ethical issues deter regulators from approving stem cell products, the ethical issues that have served as barriers to the advancement of stem cell treatments in the United States are not at play with respect to therapies like Prochymal, which uses cells derived from adult mesenchymal stem cells rather than embryonic stem cells.

Beyond procedural differences, the climate in Canada is accepting of stem cell research and commercialized products. Champions of stem cell research and commercialization include Canada's Stem Cell Network and the Centre for Commercialization and Regenerative Medicine, two entities dedicated to raising awareness and funding for stem cell-based therapies.

This culture of acceptance may translate into the regulatory domain, thereby impacting the examination and approval of stem cell drugs by Health Canada.

### IMPLICATIONS FOR INNOVATORS

For companies or scientists are ready to seek first approval for their stem cell products, the Prochymal case offers insight into the Canadian approval process. The Expert Advisory Panel for Prochymal commented that the NOC/c process, which allows certain drugs into the market without full efficacy data, “is a very innovative approach to authorize a drug into the market safely and determine its broader efficacy for a severe disease that affects a very small population.”<sup>8</sup>

Accordingly, a stem cell therapy that demonstrates similar characteristics to Prochymal may be more likely to be approved. The criteria include the following:

- The disease that the drug treats is debilitating and lethal;
- The disease the drug treats is rare and occurs in a small patient population, though it may be more prevalent in a subset of a population;
- The drug satisfies Health Canada’s safety requirements; and
- The drug’s approval is essential to be able to access greater patient populations for further confirmatory and long-term research of its efficacy.

Other stem cells therapies would be eligible to meet these criteria. Although such criteria are not the exclusive criteria for Health Canada NOC/c approval, the greatest challenge – first approval – has already been accomplished and the precedent has been set.

We believe that innovators, drug companies and patients should be hopeful that the current regulatory landscape will make Canada a destination of first choice for stem cell therapies.

### NOTES

- 1 Toni Clarke, “Prochymal approval makes Canada first country to OK stem cell therapy,” The Globe and Mail (May 18, 2012) online: <http://www.theglobeandmail.com/technology/science/prochymal-approval-makes-canada-first-country-to-ok-stem-cell-therapy/article4186797/>; Catherine Shaffer, “Canadian Stem Cell Approval Could be the First of Many,” BioWorld Today (May 21, 2012) 1; Nuala Moran, “Prochymal’s Canadian Nod Marks Stem Cell Milestone,” BioWorld Today (May 23, 2012).
- 2 Health Canada, “Report of the Expert Advisory Panel on Prochymal,” (Jan. 26, 2012) online: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapport-eng.php>.
- 3 Fiona L. Dignan, et al., “BCSH/BSBMT Guideline: Diagnosis and Management of Acute Graft-versus-Host Disease” (2012) 158 British Journal of Haematology 30.
- 4 Catherine Shaffer, “Canadian Stem Cell Approval Could Be the First of Many,” BioWorld Today (May 21, 2012) 1 at 3.
- 5 Health Canada, “Report of the Expert Advisory Panel on Prochymal,” (Jan. 26, 2012) online: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapport-eng.php>.
- 6 Minister of Health, “Guidance Document: Notice of Compliance with conditions (NOC/c),” Health Canada (June 30, 2011) online: [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/nocccg\\_accd-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/nocccg_accd-eng.pdf).
- 7 In contrast, the USFDA generally may not examine the subset efficacy of drugs in a particular patient group unless the treatment is specific to that group and disease. Although Prochymal

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is used to treat pediatric patients, it may also work in adults. Further, its stem cell properties extend its treatment potential to other diseases, such as Crohn's disease, type 1 diabetes, and radiation exposure. The result is that the USFDA evaluates Prochymal as a drug for all aGvHD patients rather than for a subset pediatric patient population only.

<sup>8</sup> Health Canada, "Report of the Expert Advisory Panel on Prochymal," (Jan. 26, 2012) online: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapport-eng.php>.



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