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# **Faster access to new drugs: Fault lines between Health Canada's regulatory intent and Industry innovation practices**

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## **Abstract**

Since 2003, Health Canada has been undergoing regulatory modernization to “ensure that Canadians have faster access to the safe drugs they need.” As national health agencies develop policies to modernize the regulation of new drugs, we examined a decade of drug approval data from the Canadian setting to see whether these policies promote innovation while maintaining safety. The drug approval data in Health Canada’s Annual Drug Submission reports between 2000 and 2010 were analysed to determine the proportion of new active substances qualifying as innovative new drugs. We also examined the proportion of successful submissions granted priority review that subsequently received safety warnings. We show that despite an increase in supplementary product submissions, there was no sustained increase in *new* active pharmaceutical or biologic products. Furthermore, priority reviews are intended to expedite new drug submissions that promise significant clinical benefits. While the proportion of submissions indicated for new active substances declined, there was a significantly higher rate of safety warnings for their priority reviews. Our results challenge the assumption that the new regulatory policies that were intended to spur industry innovation of new and safer drugs work.

## **Introduction**

On December 6, 2013, Bill C-17 was introduced in Parliament to protect Canadians from unsafe drugs.<sup>1,2</sup> If approved, its post-marketing restrictions may still arrive too late to keep unsafe drugs off the shelves from the outset. The November 2011 release of the Auditor General’s report, *Regulating Pharmaceutical Drugs*,<sup>3</sup> found that Health Canada continues to struggle with transparency and timeliness in assessing potential safety issues. Beginning in 2003 with the Therapeutics Access Strategy, Health Canada’s Health Products and Food Branch

(HPFB) established a series of initiatives to streamline the regulatory approval process that would “ensure that Canadians have faster access to the safe drugs they need”.<sup>4</sup> In this report we surveyed HPFB’s review activity between 2000 and 2010. We show that the number of innovative therapeutic products approved in Canada, measured as new active substances, has ranged from 4 to 17 percent of all therapeutic drug approvals. Furthermore, we show that 32.9% of products approved through priority review resulted in a post-market safety warning compared to 15.4% of products that were not priority reviewed. While Health Canada has put in place a series of initiatives to streamline and speed-up regulatory approval, it is important that market drivers of access and choice not be mistaken for innovation or given priority over drug safety and effectiveness.

### **Biologic reviews by Health Canada**

Since the approval of recombinant insulin in the early 1980s, biological therapeutics have emerged as innovative, effective and commercially successful products, with development and usage expected to grow further. Biologics generated \$48.2 billion (USD) in worldwide sales in 2009, compared to \$18.9 b in 2002,<sup>5</sup> and thirteen biologics are now designated as blockbuster drugs with worldwide sales over \$1 billion (USD).<sup>6</sup> Meanwhile, the Pharmaceutical Research and Manufacturers of America (PhRMA) report that there are more than 600 biotech-derived drugs currently undergoing development.<sup>7</sup> With predictions of between 8-24%<sup>8,9</sup> of biologic therapies in development ultimately being approved it is reasonable to assume that 50 to 150 of these products will come to market in the next 15 years.

The Biologic and Genetic Therapies Directorate (BGTD) of HPFB is responsible for reviewing and approving biologics, radiopharmaceuticals, and genetic therapies while the

Therapeutic Products Directorate (TPD) oversees traditional, chemistry-based pharmaceutical products. Through the policy initiatives of Health Canada's Therapeutic Access Strategy,<sup>10</sup> benchmarks of drug regulatory activity are now publicly available on the Health Canada website. These include Notices of Compliance (NOC) issued following a favourable review of the product's safety, efficacy, and quality; health advisories, warnings, and recalls (letters and notices for health care professionals and the public); product monographs, containing scientific information, safety warnings, and clinical trial results; annual and quarterly reports of review committee activity; and adverse reaction reports. We used this information to examine the regulatory trends and explore safety issues regarding therapeutics in Canada.

The number of NOCs issued by BGTD since its inception in 2000 through to the end of 2010 were obtained from Annual Drug Submission Reports from BGTD.<sup>11,12,13</sup> These annual reports provided more accurate information on NOC issuance than the NOC online database.<sup>14</sup> During this time the number of NOCs issued by BGTD for both biologics and radiopharmaceuticals increased, resulting in a backlog of submissions in review that reached its peak and was cleared in 2006.<sup>15</sup> Approximately three times the number of NOCs were issued in 2010 compared to 2000 (82 compared to 29; Figure 1). While this increase in NOCs demonstrates that the number of reviews conducted by BGTD has grown markedly, it conceals the nature of the products under review. NOCs are issued by BGTD for: i) a new drug submission (NDS), which refers to a new 'brand-name' product, and ii) a supplemental NDS (SNDS), which characterizes a change in production methods or in the usage of an existing product. From 2000 to 2010, the number of NOCs issued for NDS fluctuated yearly from 8 in 2008 to 18 in 2005 (Figure 1), with little real increase over time, while the total number of NOCs tripled, driven primarily by SNDS approvals.

A proportion of NDSs are for new active substances (NAS) that mark an innovative product whose molecular ingredient has not been previously approved in Canada. Many of the drugs that are reviewed by BGTD are for biologics whose active substance has been previously approved. For example, the formulation, manufacturing and bioequivalence of many vaccines, recombinant insulin and somatropin, and blood derived products derive from the same source molecule even though they may not truly be identical. Appropriately, these are reviewed as an NDS but not as an NAS. While the biopharmaceutical industry claims to develop new and innovative biotech-derived products, in fact, since 2000, the number of new active substances being approved, a more accurate indicator of innovative products, has remained relatively constant, with a peak of 12 NAS in 2004 (Figure 1). Despite new policies and the mandate to ensure new products are available to Canadians faster, the data show that since 2000 a substantial majority of NOCs for biologics were issued for new versions of previously approved formulations, or for manufacturing and indication changes.

### **Pharmaceutical reviews by Health Canada**

The number of NOCs issued by TPD from 2000 through to the end of 2010 were also obtained from Annual Drug Submission Reports.<sup>16,17,18</sup> In addition to reviewing NDS and SNDS applications, TPD also review abbreviated NDS (ANDS) and supplemental abbreviated NDS (SANDS), which are used for generic chemicals. Like biologics, the number of NAS approvals for synthetic pharmaceutical per year has remained almost steady, although the 14 approved in 2010 was the second lowest yearly total since 2000 (Figure 2). However, this stability has occurred while total numbers of NOCs issued by TPD has risen, driven by both ANDS and

SNDS, again suggesting that most review activity is being done on generic products or in changing the formulation or indication of existing products.

### **Priority reviews and safety concerns**

Health Canada has a priority review process to expedite the review time of medically-significant product submissions provided that the drug is “for a serious, life-threatening or severely debilitating condition where it has the potential to provide: i) effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada, or ii) a significant increase in efficacy and/or a significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies.”<sup>18</sup> Once granted a priority review, “submissions are inserted into Health Canada’s queue in accordance with a shortened review target and, as such, may be reviewed in advance of non-priority submissions.”<sup>19</sup>

The promise of new biologics creates expectations and markets.<sup>3,5,7,20</sup> Since 2000, 46.7% of biologics approved as NASs were granted a priority review, while only 21.7% of pharmaceuticals were priority reviewed by TPD in Canada (Table 1). There may well be consequences for this faster approval, however. Geizen et al report that 25% of approved biologics in the US and European Union have received a post-market safety warning.<sup>21</sup> Using the MedEffect website<sup>22</sup> to search “Dear Health Care Professional” warning letters issued in Canada since 2000, we noted a statistically significant greater percentage of warnings were issued for products granted priority review – 31.4% of priority biologics and 34.1% of priority pharmaceuticals - compared to non -priority biologics and pharmaceuticals (15% and 15.5% respectively). Despite promises for faster access, the proportion of priority reviews for NASs, both biologics and pharmaceuticals, appears to have peaked during the first half of the decade at

Health Canada. It may be that Health Canada has increased vigilance on priority reviews during the decade.

### **Fault lines between policy intent and industry practice**

Innovation in science and medicine is generated by a complex alliance of needs, desires, interests and expectations of emerging therapeutic technologies.<sup>23</sup> Regulatory activities, including product development, assessment, and policy, seek to optimize the benefits of innovative technologies while minimizing harm in both individuals and populations. With stakeholder involvement and in partnership with industry, Health Canada has put in place a series of initiatives to streamline and speed up the regulatory approval process in order to get new therapeutic products to Canadians.<sup>24,25,26,27,28</sup> At the same time, the Auditor General has criticized Health Canada for being slow to act on potential safety issues for drugs approved for market.

While a common definition of pharmaceutical innovation is still debated,<sup>29</sup> our assessment calls into question the purported *innovative* nature of the majority of biologics and synthetic pharmaceuticals gaining regulatory approval. Although industry is likely driven to have their products granted priority review there has been a decrease in the percentage of drugs, both biologic and pharmaceutical, that have been granted priority review over the past decade. At the same time there has been an expansion in the number of supplementary NDSs. Whether these trends are due to a decline in innovation or greater caution on the part of Health Canada remain to be determined.

Modernization of Canada's progressive licensing environment is resulting in faster reviews of new drugs that are approved with conditions and based on limited testing. We have shown that priority approvals result in higher post-market warnings, highlighting the need for regulators to question the meaning of innovation and the need for post-market surveillance. Off-license use continues to flourish without regulation, with a reported prevalence of 11% and with 79% lacking scientific evidence.<sup>30,31</sup> Therapeutic products in Canada must continue to be held to the highest scientific and public standards for health protection. Aggarwal suggests that the recent slowdown in the U.S. in the rate of sales of biologics (although sales still rose by 3%) is due, in part, to safety issues.<sup>4</sup> Concerns surrounding the relaxation of rigorous pre-license regulatory standards with regulatory modernization need to be addressed. Indeed, in the fall of 2011, Health Canada withdrew the approval of Avastin, a biologic that was granted a NOC with conditions, for treatment of breast cancer because of lack of efficacy. Bill C-17, *An Act to Amend the Food and Drugs Act*, introduced in Parliament on December 6, 2013, if enacted, is intended to increase Health Canada's powers to withdraw drugs after they have already been approved for market.<sup>1</sup> Real world uncertainties in safety and effectiveness, and market-driver issues of access and choice should not, however, be used to relax pre-license approval. Instead, progressive steps need to be taken by both Health Canada and the pharmaceutical industry to expand methodological rigour and limit the questionable analytical assumptions of clinical trials.<sup>32</sup> The development of sufficient and necessary tools for regulatory enforcement are of interest to us all. While Canadians may have faster access to drugs, innovative and safer products that genuinely "generate improvements in patient health"<sup>32</sup> must be the end product.

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The authors declare they have no competing interests and therefore have nothing to declare.

**Table 1.** The numbers of biologics and synthetic pharmaceuticals approved as new active substances (NASs) between 2000 and 2010, classified as to whether or not they underwent a priority review.\*

<b>Table 1</b> <b>2000-2010 NOCs with DHCP letters<sup>†</sup></b>			
	Number of NOCs issued between 2000- 2010 (% of total)	# of products with at least 1 DHCP letter issued in Canada between 2000- 2010	% of products with at least 1 DHCP letter issued in Canada between 2000- 2010
<b>Biologic</b>			
<b>NAS</b>	40 (53.3%)	6	15.0%
<b>Priority NAS</b>	35 (46.7%)	11	<b>31.4% (p=0.0065)</b>
<b>Total</b>	75	17	22.7%
<b>Pharmaceutical</b>			
<b>NAS</b>	148 (78.3%)	23	15.5%
<b>Priority NAS</b>	41 (21.7%)	14	<b>34.1% (p=0.001)</b>
<b>Total</b>	189	37	19.6%

\* Health Canada: *Notice of Compliance Database*. <http://www.nocdatabase.ca>

<sup>†</sup> DHCP=Dear Health Care Professional

**Figure 1.** The number of Notices of Compliance (NOCs) issued by the Biologics and Genetic Therapies Directorate (BGTD) for biologics and radiopharmaceuticals, based on annual performance reports.<sup>10,11,12</sup> The yellow bars indicate NOCs issued for a supplemental new drug submission (SNDS), the purple bars show those for a new drug submission (NDS), and the hatched blue bars indicate an NDS approved as a new active substance (NAS). The line graph shows the percentage of NOCs issued for a NAS in each year.

**Figure 2.** The number of Notices of Compliance (NOCs) issued by the Therapeutics Products Directorate (TPD) based on annual performance reports.<sup>15,16,17</sup> The hatched blue bars indicate a new drug submission (NDS) approved as a new active substance (NAS), the purple bars show those for a NDS, yellow for supplemental NDS (SNDS), solid green for an abbreviated NDS (ANDS), and hatched green for a supplemental ANDS (SANDS). The line graph shows the percentage of NOCs issued for a NAS in each year.

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