

# Priorities for regulatory cooperation for the North American over-the- counter drug industry

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Consumer Health | Produits de santé  
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Advancing evidence-based self-care  
Pour l'avancement des autosoins de qualité

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## 1.0 Executive Summary

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Consumer Health Products Canada (CHP Canada) and the Consumer Healthcare Products Association (CHPA) respectfully submit this brief to the Office of Information and Regulatory Affairs (OIRA) within the Office of Management and Budget in response to the US-Canada Regulatory Cooperation Council (RCC) Request for Information issued October 9th 2018 (83 FR 50689).

**Our main priority for 2018-2019 for the RCC work plans is for the U.S. Food and Drug Administration (FDA) and Health Canada to establish a Mutual Recognition Agreement (MRA) for drug Good Manufacturing Practices (GMPs).**

An MRA is the ideal regulatory cooperation project to pursue under the RCC as it serves to eliminate unnecessary, duplicative requirements that will not only result in tangible savings to both industry and government but also serve to simplify regulatory compliance and supply chains and increase economic activity between our two countries. Not only would an MRA not compromise the agency's ability to protect the health and safety of our citizens, but it would enable effective reallocation of limited inspection resources, allowing a heightened focus on drug manufacturing facilities with potentially higher public health risks across the globe. This would benefit citizens on both sides of the border and reduce adverse public health outcomes.

Now that the FDA is finalizing the transitional phase to establish an MRA with the EU, and Canada already has a longstanding MRA with the EU, it just makes sense to prioritize the development of an MRA between both the U.S. and Canada through the work of the RCC.

**Our second priority is to fulfill the objective of the 2012 OTC RCC work plan by finalizing the joint "antihistamine for the common cold" monograph.** Given that the OTC monograph reform initiative is poised to advance, it would be ideal to test the new proposed process by advancing this joint monograph that has been completed and ready for consultation since 2013.

CHPA and CHP Canada appreciate the opportunity to provide input into Health Canada and the Food and Drug Administration's regulatory reform proposals and the RCC's work plans. We look forward to continuing technical discussions about our proposals with government officials at the December 2018 RCC stakeholder forum in Washington D.C.

**Our third listed priority is the implementation of dosing information on the US Over-the-Counter (OTC) label for acetaminophen for children under 2 years old, similar to what exists in Canada.** The addition of dosing directions for children under 2 years of age can help minimize acetaminophen medication errors and overdose in the United States. Health Canada's *Regulations and Guidance Document: Acetaminophen Labelling Standard* serves as a model for appropriate dosing directions to be utilized by caregivers for children under 2 years of age.

## 2.0 Who we are

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### Consumer Health Products Canada

CHP Canada is the 120-year old national industry trade association that represents the companies that make evidence-based over-the-counter (OTC) medicines and natural health products (NHPs). These are the products you can find in medicine cabinets in every Canadian home. From sunscreens and vitamins to pain relievers and allergy medications, people use consumer health products to maintain their health and manage their minor ailments. The \$5.8 billion dollar per year consumer health product industry represents about 50,000 OTCs and 20,000 NHPs and employs approximately 57,000 Canadians<sup>1</sup>. CHP Canada is committed to working with our members, the broader health care sector, and governments for the growth of the evidence-based consumer health products market.

### Consumer Healthcare Products Association

CHPA is the 137-year old trade association representing the leading manufacturers and marketers of OTC medicines and dietary supplements that provide safe, effective and affordable therapies to treat and prevent many common ailments and diseases. Literally, from head to toe, OTCs and supplements are the trusted first line treatment for 240 million Americans every year and are recommended by healthcare providers to their patients for a range of health and wellness needs. These accessible, affordable and trusted medicines and dietary supplements empower individuals and families to meet their everyday healthcare needs. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system \$6-\$7, contributing a total of \$102 billion in savings each year. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

**Together, CHP Canada and CHPA represent 80 companies that manufacture, market and distribute OTC medicines and NHPs/ dietary supplements Canada and the U.S., with sales totalling over \$58.3 billion USD<sup>2 3</sup> in sales per year in North America.**

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<sup>1</sup> Conference Board of Canada, Healthy Growth: Estimating the Economic Footprint of the Fast Growing Consumer Health Products Industry (2015)

[http://www.chpcanada.ca/sites/default/files/healthy\\_growth\\_final\\_report.pdf](http://www.chpcanada.ca/sites/default/files/healthy_growth_final_report.pdf)

<sup>2</sup> Grand View Research: Dietary Supplements Market to Reach \$278.02 Billion by 2024 (June 2016)

<http://www.grandviewresearch.com/press-release/global-dietary-supplements-market>

<sup>3</sup> Neilsen Company OTC Retail Sales (1992-2016) <https://chpa.org/OTCRetailSales.aspx>

## 3.0 Mutual Recognition Agreement for Drug Good Manufacturing Practices

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### Issue:

- Drug Manufacturing facilities in Canada and the US are inspected on a regular basis by both the U.S. Food and Drug Administration and Health Canada, even though they are assessed against equivalent standards. When a drug product manufactured in these licensed facilities in the U.S. or Canada crosses the border, it must be quarantined and retested to the same standard, adding unnecessary costs and complexity to the supply chain.
- A Mutual Recognition Agreement (MRA) for drug GMPs between Canada and the U.S. would better align how products are manufactured and flow through global supply chains.
- While both Canada and the U.S. have established MRAs with the European Union (EU), in 2014 the RCC stepped away from its own commitment to pursue an MRA as part of its original 2012 work plan **(For more information See Appendix 1)**.

### Nature of unnecessary difference:

- Statutory requirements to ensure quality of imported products are aligned in the US ([21 U.S.C. Section 331](#)) and Canada ([Section 8 Food and Drugs Act](#)). The regulations in the U.S. ([21CFR211.165](#)) and Canada ([C.02.019 \(1-2\) of the Food and Drug Regulations](#)) also specify intervals for regular confirmatory and identity testing that must be performed to ensure conformance with GMP standards prior to release in each jurisdiction.
- An MRA for drug GMPs would establish drug GMP regulations as equivalent and allow the U.S. Food and Drug Administration and Health Canada to rely on each other's inspections and decisions.

### Why agencies should align:

- Eliminating the need to quarantine and retest products coming from Canada would: simplify regulatory compliance and supply chains, result in timelier market access for Canadians and Americans, reduce costs to industry and consumers, lead to a more effective use of inspection and administrative resources, and increase product quality in jurisdictions where saved inspection resources have been reattributed.
- CHPA and CHP Canada's recommendation is supported by the prescription drug industry, generic drug industry, and cosmetics industry.

### How agencies could align:

- Health Canada and U.S. FDA should formally commit to establishing an MRA for drug GMP inspections.
- The RCC should formally recognize previous collaborative efforts towards developing an MRA as being part of the "confidence building phase" to expedite the transition time necessary to establish such an MRA. **(See Appendix 2)**

### Estimated annual burdens on U.S. Food and Drug Administration and Health Canada as a result of unnecessary duplication:

- **Burden to FDA:** The FDA inspected 61 Canadian facilities from 2015-2016 that were already licensed and inspected by Health Canada, averaging \$1.7M- \$8.25M USD per year in

unnecessary, duplicative inspection costs for both agencies and industry. (For more information See Appendix 1).

- **Burden to Health Canada:** Health Canada inspected 7 U.S. facilities from 2015-2017 that were licensed and inspected by the FDA, averaging \$85,000- \$420,000 CDN per year in unnecessary, duplicative inspection costs for both agencies and industry.

#### **Estimated annual burden on industry that results from unnecessary duplication:**

- Elimination of direct costs of duplicative testing and quarantining products and the indirect costs of an unnecessarily complex supply chain will result in savings for industry.
  - 16 participating Canadian importers of US manufactured sunscreens saved an estimated \$4.6M CAD per year (For more information, See Appendix 1).
- Eliminating the need to quarantine products before entering either market will expedite market access by approximately 30 days per shipment, which could mitigate drug shortage concerns.
- Elimination of duplicative inspections improves manufacturing productivity by eliminating the 660-1040 extra person hours beyond daily responsibilities that are necessary to execute an inspection.

#### **Estimated annual net benefits of eliminating unnecessary duplication:**

- Reallocating resources towards inspection of drug manufacturing facilities with potentially higher public health risks across the globe will benefit patients and reduce adverse public health outcomes.
  - **Benefit to the FDA:** If resources the FDA spent on 61 inspections in Canada were instead spent in India or China during 2015-2016, it would represent a 31% and 24% increase, respectively, in inspection capabilities within these countries, where oversight is most needed. (For more information See Appendix 1).
  - **Benefit to Health Canada:** If resources Health Canada spent on the 7 US inspections were instead spent in other countries, this would represent an 18% increase in Health Canada's foreign inspection capacity.

## 4.0 Finalization of the joint monograph for “Antihistamines for the common cold”

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### Issue:

- In their 2012 RCC work plan, Health Canada and the U.S. FDA committed to developing a joint monograph “Antihistamines for the common cold.” The development work was completed and a draft of the monograph has been finalized and awaiting consultation since 2013. However, the joint consultation process has not begun due to the differences in our regulatory frameworks and competing regulatory priorities in the U.S.
- This joint effort has actually imposed U.S. regulatory barriers on Canada instead of eliminating them, preventing Health Canada from finalizing an urgently needed monograph.
- This monograph would stimulate innovation and directly result in faster access for new safe and effective product options for Canadians and Americans seeking to treat their cold and allergy symptoms.

### Nature of unnecessary difference:

- U.S. OTC monographs are codified in regulation, whereas Canadian monographs have similar force of law to guidance documents and are not subject to the same lengthy consultation process.
  - As a result of sharing information about each other’s regulatory processes through the RCC, the FDA has shifted its commitment to continue collaborating with stakeholders to coordinate and adjust their OTC development process. As a part of ongoing monograph reform discussions, the FDA has publicly stated that their monograph development system is in need of reform. CHPA has worked with FDA and with Members of Congress to craft an update to the Monograph process by which FDA could make scientific determinations for these ingredients through an administrative order process with protections for dispute resolution and issue escalation. This would let FDA follow an approach that is closer to NDA procedures, but would continue to not require an individual product approval for every product with the same active ingredient. Benefits of reform to the Monograph system include increased consumer protections, including more rapid action in the event of safety issues; increased consumer confidence; and increased consumer choice, facilitated by a system that enables innovation.
- CHP Canada and CHPA do not support the development of additional joint monographs as this requires regulatory change in the U.S. thereby hampering stakeholder engagement and extending time lines to approval. Such monographs are guidances in Canada and can undergo consultation and approval in a more expeditious manner.

### Why agencies should align:

- The finalization of a joint antihistamines monograph would result in:
  - increased product choices;
  - faster market access and decreased costs for Americans and Canadians seeking to treat their cold symptoms, and;
  - more efficient and effective use of industry and government resources.
- Finalization of the joint antihistamines monograph is supported by Canadian and U.S. industry.

### How agencies could align:

- FDA should commit to prioritize and advance the public consultation of the joint "Antihistamines for the Common Cold" monograph. In the most recent Regulatory Agenda, FDA noted that it would propose a rule adding the common cold indication to certain OTC antihistamines under the RCC in November 2018.<sup>4</sup>

### Estimated net benefits:

- The availability of OTCs creates significant value for the U.S healthcare system. OTCs generate \$102 billion in annual value relative to alternatives by savings generated from avoided doctor's visits and diagnostic testing, and drug cost savings<sup>5</sup>. Just in the case of OTCs used to treat cough, cold and flu, it is estimated that this saves the healthcare system \$4.75 billion each year<sup>6</sup>. If OTC medicines were not available, more consumers would seek prescriptions, causing a surge in office visits requiring 56,000 additional full time medical professionals.<sup>7</sup> On average, it is estimated that for every dollar spent on OTCs, it saves the U.S. healthcare system \$6-7.
- A recent U.S. study showed that more Americans are suffering from seasonal allergies and are choosing OTCs instead of prescription medications. According to the research, approximately 28 percent of Americans in 2015 reported that they suffer from seasonal allergies, with the majority of allergy sufferers (60 percent) saying they choose OTC medicines alone as their preferred treatment method. This represents a 20 percent increase from 2009. The study also showed 75 percent of allergy sufferers purchased an OTC medication either on their own or in addition to a prescription treatment in 2015, compared to just 66 percent in 2009, suggesting that consumers have adjusted their behavior as more OTC options have become available over the past several years.<sup>8</sup>

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<sup>4</sup> <https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201810&RIN=0910-AF31> (accessed October 23, 2018)

<sup>5</sup> Booz & Co The value of OTC medicines in the United States (2012) <http://www.yourhealthathand.org/images/uploads/The Value of OTC Medicine to the United States BoozCo.pdf>

<sup>6</sup> Lipsky, Northwestern University (2004) <http://www.yourhealthathand.org/images/uploads/Affordability-Jun2011-updated2.jpg>

<sup>7</sup> Booz & Co The value of OTC medicines in the United States (2012) <http://www.yourhealthathand.org/images/uploads/The Value of OTC Medicine to the United States BoozCo.pdf>

<sup>8</sup> Nielsen and CHPA, Assessing Consumer Benefits of Allergy Rx-to-OTC switches, 2017 <https://www.chpa.org/2017CHPANielsen Allergy OTC White Paper.aspx>



## 5.0 Consistency regarding availability of dosing information on the Over-the Counter (OTC) label for acetaminophen for children under 2 years old

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### Issue:

Acetaminophen is a commonly recommended and used antipyretic and analgesic medicine for young children and infants in both Canada and the United States (US). There is a clear medical and caregiver need for acetaminophen medicines in the pediatric population, including children under 2 years of age. The Canadian Food and Drug Regulations and an associated Guidance Document: Acetaminophen Labelling Standard expressly permit labeled dosing directions for ages 0 months and older for OTC infants' pediatric acetaminophen products (80mg/ 1mL). However, consumer facing dosing instructions in the US are not available for children under age 2 on the OTC Drug Facts Label for pediatric acetaminophen products. Instead, in the US caregivers are instructed to consult their doctor. The lack of dosing information on the US OTC label for children under 2 years of age is burdensome for caregivers and health care professionals and has contributed to medication errors and acetaminophen overdose in the US.

### Nature of unnecessary difference:

- US OTC monographs are codified in regulation, whereas Canadian monographs have similar force of law to guidance documents and therefore can be revised more readily in response to new data or emerging issues.
- In Canada, labelled dosing directions for children under 2 years and down to 0 months is supported by the *Regulations*. Consumer facing labels for infant acetaminophen products typically provide direction for ages 4 months and above.
- In the US, acetaminophen follows the Food and Drug Administration (FDA) monograph system, and the current US OTC label (per the internal analgesic monograph) only provides dosing for children 2 years and older. Caregivers are instructed to consult a doctor for ages under 2 years.
- Summary of previous FDA consultation and correspondence on this topic to date:
  - In 1997, the FDA Nonprescription Drugs Advisory Committee (NDAC) unanimously recommended that acetaminophen be labeled for ages 6-24 months.
  - In 1999, McNeil (Johnson & Johnson Consumer Inc) submitted a Citizen Petition to request amending the directions under the Tentative Final Monograph for children under 2 years
  - In 2008, CDER Acetaminophen Hepatotoxicity Working Group recommended inclusion of dosing instructions for children < 2 years on the OTC Drug Facts Label. This recommendation was shared with the advisors at the 2009 Joint Meeting of Drug Safety and Risk Management, Nonprescription Drug and Anesthetic and Life Support Drugs Advisory Committees regarding acetaminophen-related overdose and liver injury.
  - In 2011, FDA convened a Joint Meeting of the NDAC and the Pediatric Advisory Committee regarding adding new dosing information for oral OTC drug products containing acetaminophen to the label for children less than 2 years of age. In response to the question "Do the pharmacokinetic (PK), safety, and efficacy data support the addition of new labeled dosing directions corresponding to a 10-15

mg/kg dose for children 6 months to 2 years of age?”, the committee vote was: Yes: 21, No:0 and Abstain:0

- In 2013, the Consumer Healthcare Products Association (CHPA) submitted a Citizen Petition to FDA in support of labeling for acetaminophen dosing for children ages 6 months to 2 years.

Related US OTC analgesic products with <2 years of age dosing:

In April 1999, FDA approved dosing directions on the consumer OTC label for children 6 to 23 months of age for McNeil Consumer Healthcare’s OTC Infants’ MOTRIN® (ibuprofen) product. The FDA approved dosing schedule for OTC pediatric ibuprofen includes both weight-based and age-related dosing with a dose increment for 12-17 lbs. body weight and ages 6-11 months and a dose increment for 18-23 lbs. body weight and ages 12-23 months.

In April 1980, FDA approved the Type 5 – New Formulation or New Manufacturer submission for an over-the-counter acetaminophen suppository under NDA 018337. Current labeling supports dosing as young as 6 months.

- As stated above, CHPA has worked with FDA and members of Congress on issues of monograph reform. CHPA and CHPC recommend that the topic of acetaminophen dosing directions for under 2 years, which directly addresses safety concerns for medication errors and acetaminophen overdose, be prioritized under the reformed monograph system.

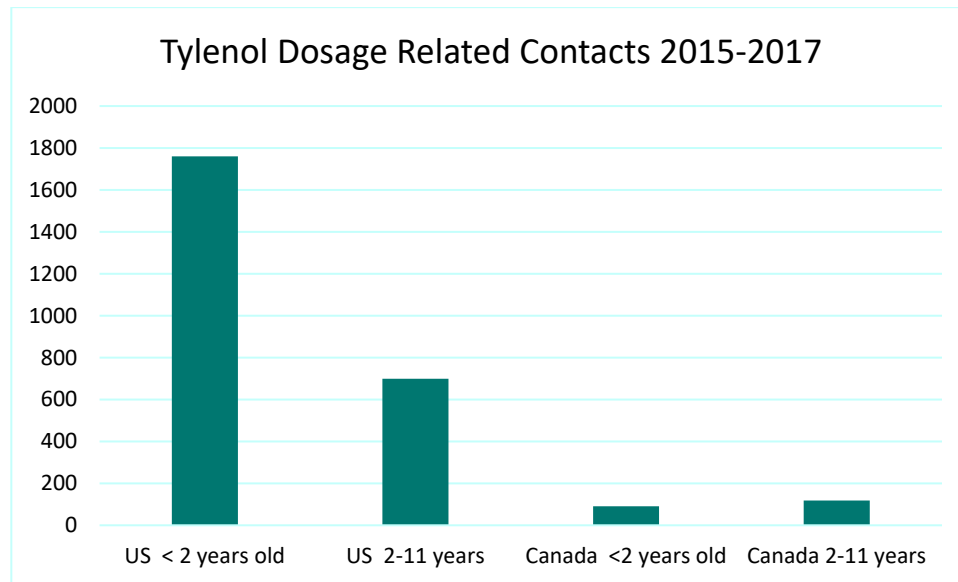
#### Why agencies should align:

The implementation of US OTC acetaminophen dosing for children under age 2, similar to what has existed in Canada for years, is an important element in reducing medication errors and acetaminophen overdose, is supported by the pediatric healthcare community including the American Academy of Pediatrics<sup>1</sup>, American Academy of Family Physicians<sup>2</sup>, American Pharmacists Association<sup>3</sup>, American Association of Poison Control Centers<sup>4</sup>, and is consistent with previous FDA Advisory Committee reviews of the proposal.

Expanding the US OTC label to include acetaminophen dosing directions for children under 2 years of age can help minimize medication errors in the following ways:

- Helps caregivers find the correct acetaminophen dose to give to their child;
- Reduces the need for caregivers to call a doctor, a friend, or a relative, to search the internet for an acetaminophen dose, to rely on their limited recall of previous dose recommendations, or guess at the dose; and
- Allows caregivers to confirm the acetaminophen dose when provided by the doctor or other healthcare professional.

To showcase the differences in the numbers of dosage related questions received between Canada and the US, Johnson & Johnson Consumer Inc. compiled call center metrics across the past 3 years for contacts coded as “dosing” or “how to use” for acetaminophen products for children less than 12 years. In the US, where dosing is not available for children under 2 years of age, the dosage related contact rates for those 2 years of age were more than 2.5X higher than the number received for ages 2-11 years (1760 vs 699). In Canada, the total numbers are similar between the two age groups (91 vs 118). When inquiries are received by the company in the US, caregivers are directed to contact their child’s health care provider as off label dosage directions for the under 2 age group may not be provided.

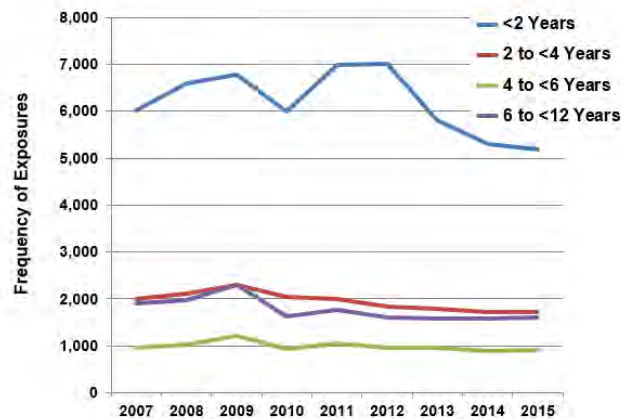


When information is not available on the label, caregivers turn to unconfirmed sources for dosing information. On average there are an estimated 100,000 monthly internet searches for relevant keywords for acetaminophen dosing under age 2. A “Google” search conducted between June 5-21, 2018 for “Acetaminophen dosing for children under 2 years of age,” yielded 29.6 million results. Looking at a subset of 200 sites, 122 of those reviewed contained dosing for children under 2 years of age. Key concerns identified in the search included:

- Even though the 80 mg/0.8 mL concentrated formulation is no longer marketed in the US:
  - 30 sites provided dosing for 80 mg/0.8 mL & 160 mg/5 mL formulations
  - 22 sites provided dosing for concentrated drops (80 mg/0.8 mL)
- 1 site provided dosing for “chewable tablets” for ages 12-24 months
- 59 sites provided dosing recommendations in only mL, 40 sites provided dosing in mL & teaspoons, 5 sites for only teaspoons, and 4 sites provided dosing in only milligrams
- Less than half recommended the use of an appropriate dosing device
- Max daily dose, frequency of dosing, and other warning information varied by site

US surveillance characterized ongoing contributing factors to medication errors in children under age 12 for single ingredient acetaminophen. The following graph showcases single ingredient acetaminophen medication errors from the National Poison Data System (NPDS) over the years 2007-2015. For each of the years shown, the number of medication errors in children under 2 years of age accounts **for more than half** of the total number of medication errors under 12 years<sup>5</sup> of age.

### Medication Error Exposures by Age Group



Follow up surveys for a subset of the above cases, and additional cases through 2016, revealed

that >20% of *caregivers rely on the packaging* of the product for children <2 years of age even though the *OTC Drug Facts Label does not contain dosing directions* for this age group<sup>6</sup>. Select verbatims<sup>5</sup> of how caregivers used packaging to determine dosing directions included:

- “Thought the concentration labeled on the front was the intended dose.”
- “Mom thought 5mL’s was the dose but decided to give half that amount since this was a baby.”

#### How agencies could align:

- FDA should commit to prioritize and advance adding labeled dosing directions for acetaminophen products for children under 2 years of age, looking to Health Canada’s *Regulations and Guidance Document: Acetaminophen Labelling Standard* as key references.

#### Estimated net benefits:

From 2007-2015, **38,125 single ingredient liquid acetaminophen medication errors** were reported from the US NPDS for children under 2 years of age<sup>5</sup>. We believe that additional appropriate directions to the US labeling could prevent a substantial number of these cases. With the cost per call at a poison center estimated from \$43- over \$100, the 38,125 medication error reports above represent from \$1.6MM to over \$3.8MM in health care costs<sup>7-9</sup>.

While most of those cases were treated through consultation with the Poison Center, **1449 cases were referred to a Health Care Facility** for treatment (1074 treated/evaluated and released, 147 admitted to non-critical care unit, 50 admitted to a critical care unit and 178 other/unknown). **Treatment for each report referred to a Health Care Facility might cost from \$100 to upwards of over \$10,000 depending on the severity of the case**<sup>10-11</sup>.

This is not a complete summary as not all medication errors are captured within the NPDS and other patients may present directly for treatment. Additional communication of dosing information for caregivers of children <2 years of age, placed directly on the OTC Drug Facts Label, could prevent both the emotional and monetary health care costs related to acetaminophen medication errors in children under 2 years of age.

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  11. <https://health.costhelper.com/emergency-room.html>
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## 6.0 Conclusion

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Regulatory cooperation is good for governments, business and citizens, whether they are consumers, entrepreneurs, employees or patients.

The Canada-US Regulatory Cooperation Council provides the ideal banner to advance ambitious projects seeking to enhance harmonization and eliminate unnecessary costs. CHPA and CHP Canada and the broader drug industry agree that establishing a Mutual Recognition Agreement for drug GMPs would be the ideal project to achieve meaningful collaboration, and savings for industry, governments and citizens.

We also seek to finalize an original project conceived under the RCC by consulting on and finalizing the joint OTC antihistamine monograph. Although this project did not achieve the intended success due to the regulatory differences in our two systems, the RCC provided a mechanism to explore these differences and guide regulatory reform agendas for OTCs on both sides of the border.

The implementation of US OTC acetaminophen dosing for children under age 2, similar to what exists in Canada, is a necessary step in reducing pediatric acetaminophen medication errors and overdose, is supported by the pediatric healthcare community and is consistent with previous FDA Advisory Committee reviews of the proposal.

# Appendix 1: Briefing Note: Mutual Recognition Agreement for pharmaceutical good manufacturing practices between Canada and the U.S.

*(For Information only)*

## Summary:

- While both Canada and the U.S. have established Mutual Recognition Agreements (MRAs) with the European Union (EU), in 2014 the Canada-U.S. Regulatory Cooperation Council (RCC) stepped away from its own commitment to pursue an MRA as part of its original 2012 work plan.
- Between 2015 and 2016, this lack of an MRA has cost both governments as much as \$17.3 million in unnecessary, duplicative inspections, diverting finite inspection resources away from areas of the world that may pose a much higher risk.
- The renewed commitment in the Canada-U.S. RCC provides the ideal opportunity to gain a formal commitment from the Canadian and U.S. governments to establish an MRA and to immediately enter the “Mutual Reliance” phase, allowing Health Canada and FDA drug inspectors to rely upon information from drug inspections conducted within each other’s borders.

## Background & Context

### Consumer Health Products Industry:

Consumer health products are items used every day to maintain health and manage minor ailments. These products include over-the-counter drugs such as pain relievers and allergy medications, and natural health products such as vitamins and supplements.

The Consumer Healthcare Products Association (CHPA) is the 137-year old trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements in the United States. Consumer Health Products Canada (CHP Canada) is the Canadian national industry association representing manufacturers of evidence-based non-prescription medicines (OTCs) and natural health products (NHPs).

In the U.S, the OTC industry has grown over 160% in the last 10 years and is estimated to generate \$40 billion in sales. Research has shown that every dollar spent by consumers on OTC medicines saves the U.S. healthcare system \$6-\$7, contributing a total of \$102 billion in savings each year. In Canada, domestic and international sales of consumer health products have also increased rapidly over the last decade, compared to overall retail sales. From 2004 to 2014, total retail sales across the country grew at an average annual pace of 3.8 per cent while consumer health products sales increased by 4.2 per cent per year. In 2014, domestic retail sales of consumer health products were valued at \$5.6 billion, while exports were estimated at \$1.5 billion. Between 2004 and 2014, exports

of these products nearly doubled - an increase of almost three-and-a-half times the growth in overall exports. Overall, the Canadian industry makes a \$5.8 billion contribution to GDP and supports almost 57,000 jobs.

## Issue

Many of CHPA's and CHP Canada's and members are global multi-national companies based in the U.S. who are seeking better global alignment and regulatory harmonization regarding manufacturing processes.

### **Mutual Recognition Agreements (MRAs):**

The role of an MRA for good manufacturing practice (GMP) inspections is to encourage greater international harmonization, make more efficient use of inspection capacity and reduce duplication. Canada has an MRA with the E.U. for drug GMP inspections, which for some EU states began in 2003. This allows both regulators to rely on each other's inspections, reduces duplicative efforts, lowers costs and allows inspection resources to be focused on areas of the world that may pose a greater risk due to noncompliance with GMPs.

The 2012 Canada-U.S. Regulatory Cooperation Council (RCC) Work Plan committed Health Canada and the U.S. FDA to increase mutual reliance on each other's routine surveillance of GMP inspection reports of manufacturing facilities for drugs and personal products, rather than having to conduct duplicative inspections in each country. However, in the 2014 RCC Work Plan, Health Canada and the U.S. FDA backed away significantly from this commitment and instead decided to simply continue to engage in existing multi-lateral forums on drug GMP inspections.

At the same time as the RCC was downgrading its joint commitment, the U.S. FDA and the E.U. were engaged in a mutual reliance initiative collaborating to evaluate the way each regulatory body inspects drug manufacturers and assesses the risk and benefits of an MRA. In March 2017, the U.S. FDA and the E.U. announced the MRA for drug GMP inspections, which entered into force on November 1, 2017 and will be in the transition phase until July 2019.

## Current Status

Despite the fact that OTCs are manufactured in Canada and the U.S. to similar GMP requirements and similar protections, and that both Canada and the U.S. have entered into MRAs with the E.U., the lack of an MRA between Canada and the U.S. means that both regulators need to inspect the same facility making products destined for each country. Not only are facilities being inspected twice, when products cross the border, the same confirmatory testing needs to be repeated, adding costs, discouraging trade and creating delays for consumers to access new products.

Currently, the RCC work plans only commit Health Canada and the FDA to continue participation in existing multi-lateral forum such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S), International Conference on Harmonization (ICH), the International Pharmaceutical Regulators Forum (IPRF), and the International Coalition of Medicines Regulatory Authorities (ICMRA) to achieve closer cooperation with other jurisdictions. While this commitment is important, not addressing specific areas for cooperation between Canada and the U.S. undermines the attainment of the RCC objectives to produce tangible benefits to trade between Canada and the U.S.



The recently negotiated United States-Canada-Mexico Agreement (USMCA) [Pharmaceutical Annex](#) establishes a need for both the U.S and Canada to avoid unnecessary duplicative regulatory requirements (Article 12.F.3 (2)) and improve collaboration on drug inspections (Article 12.F.5 (3)) beginning with a requirement to establish mechanisms to permit the exchange of confidential information relevant to drug inspections, including GMP inspection reports (Article 12.F.5 (4)). Establishing a confidentiality agreement is the necessary precursor to establish an MRA as it would allow both agencies to make a decision based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

## Considerations & Impacts

### Policy Alignment:

- Pursuing an MRA for GMP inspections between Canada and the U.S. aligns directly with the objectives of the RCC. These objectives continue to be a commitment from President Donald J. Trump and Prime Minister Justin Trudeau as evidenced in a joint statement, as well as the U.S. government direction to reduce regulatory burden and control regulatory costs.
- Aligning inspection decisions is one of the most important initiatives to avoid unnecessary differences between Canada and the U.S. It would create shared, tangible regulatory outcomes that are business-friendly, reduce costs, and increase economic efficiency without compromising health, safety and standards.

In 2012, the U.S. Congress passed the *Food and Drug Administration Safety and Innovation Act* giving the FDA authority to enter into agreements with foreign regulators to recognize drug inspections that are capable of meeting U.S. requirements.

In the 2011 *Special Report: Pathway to Global Product Safety and Quality*, the FDA outlined their vision for the next decade recognizing that product safety and quality no longer begin or end at the border. This report stated that it is not feasible for the U.S. FDA to inspect every high risk international pharmaceutical facility and that there is a need to partner closely with foreign regulators to share information, effectively allocate resources based on risk, and leverage efforts of other government coalition members, industry and third parties. Health Canada committed a similar approach to collaborate with international regulatory partners in a 2015 *Annual Inspection Summary Report*. Over 80% of health products are imported into Canada, and as the global supply chain continues to expand with companies producing more products around the world, Canadians are exposed to greater risks via products manufactured in countries with little regulatory oversight.

### Resource Implications:

- An MRA for drug GMP inspections between Canada and the U.S. would result in cost savings for both regulators, without compromising health and safety. This would allow both governments to more appropriately reallocate limited inspection resources to international jurisdictions where there isn't the same level of confidence, resulting in an enhanced ability of regulators to mitigate the greatest potential risks to Canadian and U.S. consumers.

### Savings to regulators and industry due to elimination of duplicative inspections

- The FDA inspected 26 Canadian facilities in 2016 and 35 in 2015 that were already licensed and inspected by Health Canada.
  - Based on the annual generic pharmaceutical user fees for [foreign finished dosage form facilities](#), (which cover 56% of the recovery costs for personnel and a premium

for foreign inspections) we estimate the cost of one inspection and administrative licensing can range from \$59,000- \$273,000 USD.

- We estimate the inspections carried out over the last two years cost the FDA and the industry each: \$1.5M- \$7M USD in 2016 and \$2M-\$9.5M USD in 2015.
  - In 2015-2016, out of the 28 E.U. countries that the U.S. has just established an MRA with, Canada ranks third for most FDA inspections behind Germany (120 FDA inspections) and Italy (77 FDA inspections) during that same time, indicating an MRA with Canada would provide value compared to EU countries. If these resources for 61 foreign FDA inspections were instead spent in India or China during that same time period, it would represent a 31% and 24% increase in inspection capabilities within these countries, where oversight is most needed.
- Health Canada inspected 5 U.S. facilities in 2016 and 2 in 2015.
    - Based on the annual [2016 fees for Drug Establishment Licenses](#) (which cover the review of an application, annual reviews, amendments and domestic and foreign inspections) and with domestic inspections occurring every 3 years, we estimate the cost for one inspection and administrative licensing to range between \$25,000-\$120,000 CDN, which represents 61% of the recovery costs for Health Canada.
    - We estimate the inspections conducted over the last two years cost Health Canada and the industry each: \$125,000-600,000 CDN in 2016 and \$50,000-\$240,000 CDN in 2015. This represents approximately 18% of Health Canada's limited resources for foreign inspections, as a total of 11 and 28 inspections took place in 2016 and 2015 respectively.
  - Although industry would need to continue to pay the above licensing fees for foreign facilities regardless of whether the site is in an MRA country, tangible savings would result due to the elimination of duplicate inspections. Preparation for and conducting an inspection represents an investment of 660-1040 extra person hours, beyond daily responsibilities.

#### **Review Resource efficiencies**

- With an MRA, only a valid Certificate of Compliance from the other regulator is required to demonstrate site compliance, which requires minimal review. This would eliminate the need to review large files, including Exit Inspection Reports, responses, SOPs and Site Master Files.
  - Annually, Health Canada receives over 400 Certificates of Compliance from its MRA partners and reviews close to 500 inspection reports for foreign sites not in MRA countries.

#### **Savings to industry due to elimination of duplicative confirmatory testing**

- With an MRA, it would no longer be necessary to quarantine and immediately retest products coming from a licensed facility in the other country. The costs of retesting products can range up to \$190,000 per product per shipment annually, depending on the type of testing required. As a result of these costs, some products are never launched in Canada due to limited availability of Canadian testing labs that have completed verification of the required test methods. Eliminating duplicative testing will also shorten release times, enabling consumers on both sides of the border faster access to new treatment options.
- Canada has already engaged in a pilot program that has contributed to building trust with industry and increased confidence in the long-term objective of establishing an MRA between Canada and the US.

- The sunscreen pilot outlined in the 2016-2017 RCC work plan established a mechanism for Canadian importers of US manufactured sunscreens to waive the requirement in [C.02.019 \(1-2\) of the Food and Drug Regulations](#) to perform identification testing of each lot and annual confirmatory testing. To participate, it must be demonstrated that the US manufacturer is compliant with GMPs and has been inspected by the FDA within 5 years.
  - 16 companies representing 270 OTC DINs have participated in the pilot resulting in significant savings to the industry (**See Table 1**).
  - Health Canada has audited the pilot process and determined it was a success and plans to expand the scope of the pilot to include more products in 2019.

**Table 1: Estimated savings to Canadian importers of US manufactured sunscreens through participating in the RCC sunscreen pilot**

Element	Estimated Cost per DIN/ year	Extrapolated costs for 270 OTC DINs participating in the pilot (16 participating companies) as of October 2018
<b>Assumptions</b>		
# of Shipments/ year	5 Shipments/ year	5 Shipments/ year x 270 DINs = 1,350 Shipments/ year
Average batch size/ shipment	55,000 Units	55,000 Units x 1,350 shipments/year = 74,250,000 Units
# of pallets/ shipment	8 pallets/ shipment	10,800 pallets
<b>Direct costs</b>		
Annual Confirmatory testing and ID testing per shipment	\$1,500/shipment X 5 shipments = <b>\$7,500</b>	\$1,500/shipment X 1,350 shipments= <b>\$2,025,000</b>
Average # days stock can be released earlier due to lack of confirmatory testing/ shipment	27 days X 5 shipments = 135 days saved	27 days X 1,350 shipments = 36,450 days saved
Cost savings for average storage/warehouse costs for 1 month of product quarantine for 1 shipment (of 8 pallets)	\$80 X 5 shipments = <b>\$400</b>	\$80 X 1,350 shipments = <b>\$108,000</b>
Storage cost savings due to avoided Known Laboratory Errors (KLE) by CDN contract who infrequently test a certain dosage form) results in average delay of 1 week	(\$80/4= \$20 per shipment) X 3 KLE/ year= <b>\$60</b>	3 KLE/year X (\$20/ shipment) X 1,350 shipments= <b>\$81,000</b>
<b>Total direct cost savings for pilot participants</b>	<b>\$7,960</b>	<b>\$2,214,000</b>
<b>Indirect costs</b>		
Costs of 1 month storage when establishing safety stock levels	<b>\$400</b>	\$400 x1,350 shipments = <b>\$540,000</b>
Costs due to management and oversight of outsourced/third party testing laboratories	2 FTE X \$60,000= <b>\$120,000</b>	2 FTE x 16= 22 FTE, or <b>\$1,920,000</b>
<b>Potential indirect cost savings for pilot participants</b>	<b>\$120,400</b>	<b>\$2,460,000</b>

Total possible savings of <u>direct and indirect</u> costs for sunscreen pilot participants	\$128,360	\$4,674,000
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## Recommendation:

- CHP Canada and CHPA’s recommendation (which is supported by the prescription drug industry, generic drug industry, and cosmetics industry) is that, under the Canada-U.S. RCC, both governments formally commit to establishing an MRA for drug GMP inspections.
- We further recommend that the RCC formally recognize the past years’ work together as being part of the “confidence building phase” and therefore expedite the transition time necessary to establish such an MRA.

## Appendix 2: Process and progress towards developing an MRA for drug GMPs between U.S and Canada

Step #	Element	Description	
1	Preliminary proposal for an MRA	Proposal initiated by one party. Consensus by both parties on agreement to proceed. <b>Note:</b> RCC 2012 Work Plans included joint agreement to proceed with Mutual Reliance on each other's routine surveillance of GMP inspection reports of manufacturing facilities for drugs and personal products, rather than having to conduct duplicative inspections in the other country.	
2	Confirmation of collaboration	Communication confirms intent to pursue an MRA development	
3	"Confidence Building Phase"  GMP Compliance program assessment	Determine equivalency of GMP compliance program based on:	
		<b>Element</b>	<b>Status</b>
		Confidentiality agreement established to share information	<b>2012 work plan achievements:</b> <ul style="list-style-type: none"> <li>Platform to exchange inspection information regarding sites of joint interest</li> <li>Exchange major regulatory actions, inspection schedules bilaterally and through PIC/S</li> </ul> <b>Article 12.F.5(4)USMCA requires Canada and the US to establish mechanisms to share confidential information relevant to drug inspections, including unreacted GMP inspection reports.</b>
		Documentation review	<b>2012 work plan achievements:</b> <ul style="list-style-type: none"> <li>Criteria for GMP observational inspection and assessment tools developed by both agencies</li> <li>Assessment of legislation, policies, guidance, training records and SOPs potentially outstanding</li> </ul>
		Evaluation of processes and procedures including on-site evaluations	<b>2012 work plan achievements:</b> <ul style="list-style-type: none"> <li>Confidence building exercise to develop greater understanding of each agency's respective regulatory system and operational framework</li> <li>Four observational joint inspections conducted</li> </ul> <b>2015-2017 work plan achievements:</b> <ul style="list-style-type: none"> <li>Conduct joint inspections of foreign sites of interest through PIC/S</li> </ul>
		Reporting an assessment	<b>2012 work plan achievements:</b> <ul style="list-style-type: none"> <li>Both agencies acknowledge similarities in inspection approach and GMP principles</li> <li>Differences exist in inspectional practices</li> </ul>
	Confirmation of equivalency		
4	Prepare the working draft MRA	Parties prepare a working draft of the MRA. <b>Note:</b> Text of <a href="#">FDA-EU MRA</a> and <a href="#">Canada-EU MRA</a> could be leveraged as a starting basis for discussion.	
5	Signature	Canada: Policy approval by Cabinet US: Approval by US Trade Representative	
6	Tabling treaty	Canada: Canadian Minister of Foreign Affairs initiates tabling of the MRA in Parliament. US: US Department of Commerce, International Trade Administration, Foreign Commercial Service	
7	Ratification	Depositing of the instrument of ratification	