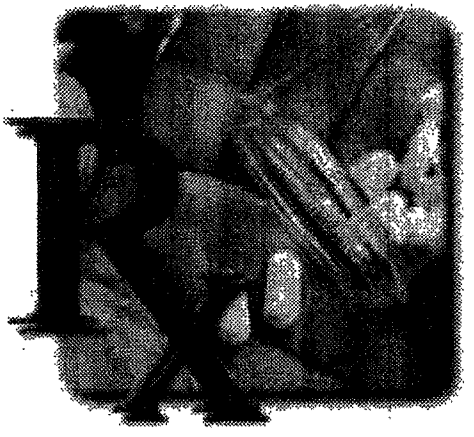

# Report On Feasibility Of Employees And Retirees Safely And Effectively Purchasing Prescription Drugs From Canadian Pharmacies

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**October 27, 2003**

**Rod R. Blagojevich, Governor of Illinois**

# Table of Contents


| | |
|---|---|
| **Executive Summary** | **Page 1** |
| **Issue Overview** | **Page 6** |
| **Research Method and Design** | **Page 8** |
| **Research Findings** | **Page 11** |
| **Options Analysis** | **Page 24** |
| **Summary** | **Page 30** |
| **Appendices** | **Page 31** |

## Executive Summary

# Can State employees and retirees obtain safe and effective prescription medications at lower overall cost by purchasing from Canadian pharmacies?

October 2003

This analysis addresses the feasibility of enabling participants in the State of Illinois' employee and retiree health benefit programs to purchase a specified set of prescription medications from Canadian vendors. The central issue of this analysis is whether State employees and retirees can obtain safe and effective prescription medications at lower overall cost by purchasing from Canadian pharmacies.

Like most employers, the State of Illinois has experienced dramatic increases in pharmacy benefit expenditures for participants in its employee and retiree health benefit programs. And, like any other employer, the State has reviewed its plan design, negotiated with providers for favorable prices, and increased employees' and retirees' cost sharing obligations. In spite of these cost-saving strategies, expenditures for State employees' and retirees' prescription medications have increased approximately 15% each year for the past five years. This trend is expected to continue as technology continues to provide new and improved pharmacological solutions to manage acute and chronic illnesses, and as the population ages.

Purchasing pharmaceuticals from Canadian sources may provide an important opportunity to reduce costs and extend the purchasing power of employees and retirees to better afford prescription drugs. Favorable exchange rates, Canadian pharmaceutical pricing and distribution practices can make medications needed by employees and retirees available at far less cost to the State than current practice allows.

The analysis draws extensively on information gathered through research, by soliciting the views of major organizations and associations within the United States' pharmaceutical industry, and through a fact-finding visit to several of Canada's major pharmaceutical providers arranged by the Office of the Special Advocate for Prescription Drugs. The State of Illinois delegation included leadership staff representing:

- Office of Special Advocates for Prescription Drugs
- Director of the Department of Public Health and the State's Chief Medical Officer
- Assistant Director of Public Health
- Pharmacist with the Department of Public Health
- Legal Counsel, Department of Professional Regulations
- Prosecutor, Department of Professional Regulations
- Director of Drug Compliance, Department of Professional Regulations
- Policy Analyst, Office of the Governor
- Counsel, Office of the Governor

Acknowledgements and key documents and supporting materials are provided in the Appendices to this report.

The research process was as comprehensive as possible, exploring the following five issue areas.

- Consumer Safety
- Regulatory Governance
- Program Drugs (Pharmaceuticals Appropriate for Coverage)
- Projected Cost Savings / Reduction in Benefit Expenditures
- Policy and Economic Impact

## Key Findings

- Employees and retirees can safely purchase drugs from Canada.
- Pharmacy practice in Canadian provinces of Manitoba and Ontario is equal to or superior to pharmacy practice in the State of Illinois.
  - Prescription medications dispensed in Canada is mainly in "unit of use" sealed packages, shipped directly from the manufacturer. Manufacturer sealed, Unit of Use packages dramatically reduce the possibility of medication errors and counterfeiting.
  - The provincial regulatory systems in Manitoba and Ontario provide substantially equivalent protection for the health and safety of the public as is provided for in the State of Illinois.
  - Though not identical in statutory or regulatory text, both countries' methods of ensuring safety and efficacy of prescription drugs are comparable.
  - Canada's system for the pricing and distribution of pharmaceuticals is less likely than that of the system in the United States to foster drug counterfeiting.
  - The United States and Canada have comparable requirements at virtually every level for the warehousing and storage of pharmaceuticals.
  - The educational requirements and professional regulation of licensed pharmacists in the Canadian provinces visited are as rigorous as those of Illinois.

- The pharmaceutical manufacturing, storage, distribution and dispensing requirements under Canadian law are substantially equivalent to those requirements under federal regulations in the United States.
- Pharmacists participating in the fact-finding delegation observed that incident reporting of internal process errors was more rigorous in the Canadian provinces of Manitoba and Ontario than in the State of Illinois.

- A formal program to purchase prescription drugs from Canadian pharmacies is likely to impact retail pharmacies in Illinois. This impact can be minimized and patient safety enhanced by implementing a Primary Care Pharmacist (PCPh) Model.

**Proposed Recommendation:**

- In order to maximize participation and savings we recommend that the State:
  - Contract with a non-domestic Pharmacy Benefits Manager (PBM) or similar entity
  - Establish a Primary Care Pharmacist (PCPh) Model
  - Require the employees and retirees to pay only the shipping cost for drugs obtained from Canadian sources.

- Recommend that the Governor direct the department of Central Management Services (CMS) and the Office of the Special Advocate for Prescription Drugs (OSAPD) to contract with a vendor as soon as practicable and target implementation of Caremark enrollment under the Quality Care Health Plan (QCHP) on April 1, 2004 for a limited number of drugs (more restricted than the recommended list of drugs for this program detailed in Appendix A-2). The complete list of drugs for this program is recommended to be available on July 1, 2004.

- To enhance patient safety, we further recommend an ingredient and quality assurance-testing program be implemented. The State would work with Illinois Department of Public Health and the University of Illinois (UIC) Chicago College of Pharmacy to test drugs to ensure quality of both the domestic and non-domestic drug supply purchased by employees and retirees.

**Cost Savings Projections**

The following cost savings projections are divided into the two major health care programs provided by the State. Approximately half of the employees and retirees are enrolled in the Quality Care Health Plan (QCHP) administered by Caremark, Inc., the other half are enrolled in one of nine Managed Care Plans administered by seven separate companies.

Quality Care Health Plan (QCHP) Participants:

The projected 12-month savings for this group is $55,000,000.This projection assumes all eligible prescriptions are filled through the proposed Canadian Mail Order Plan (CMOP) detailed as **Option 5** in the report. The variables include the currency exchange rate, manufacturer price increases, and the level of employee/retiree participation.

- $20.7 million would be savings to the plan members in the form of waived co-payments.
- $34.3 million would be the savings to the State due to lower drug costs.

Based on current domestic mail order participation rate of approximately 7% of eligible prescriptions, we would estimate a participation rate of at least 33% given the extremely small, proposed out-of-pocket cost to the participant. At the assumed rate of 33%, the total savings (employees, retirees and State) would be $18,300,000 for the first full year of Canadian Mail Order Plan.

- $6.9 million would be savings to the plan members in the form of waived co-payments.
- $11.4 million would be the savings to the State due to lower drug costs

Managed Care Plans – Currently administered by seven different Managed Care Organizations:

At present, the prescription drug benefit provided to the employees and retirees in the Managed Care Plans are considered "carved-in". The recommendation below assumes these drug benefits would be "carved-out" of the Managed Care Plans and consolidated with the drug spend under the QCHP Plan. The process of carving out the drugs from the Managed Care Plans would require additional time to implement and is detailed latter in the report.

Assuming the drug benefits were carved out of the Managed Care Plans, the projected 12-month savings for this group is $35,700,000 (employees, retirees and State). This projection assumes all eligible prescriptions are filled through the proposed Canadian Mail Order Plan. The variables include the currency exchange rate, manufacturer price increases, and level of employee/retiree participation.

Due to lower employee and retiree co-payments in Managed Care Plans, the amount saved by the State would be proportionally higher than the amount saved by the employees and retirees.

The table below illustrates the potential co-payment savings to employees and retirees under the proposed Canadian Mail Order Plan

| | Quality Care Health Plan Administered by Caremark, Inc. | | Managed Care Plans | |
|---|---|---|---|---|
| | Formulary Brand Drugs | Non-formulary Drugs | Formulary Brand Drugs | Non-formulary Brand Drugs |
| Annual co-payment for three prescriptions at retail | $504 | $1008 | $180 | $360 |
| Annual co-payment for three prescriptions through domestic mail order (2 co-payments for 3 months supply) | $336 | $672 | $120 | $240 |

Under the proposed Canadian Mail Order Plan, a current participant in the Caremark administered plan, getting three non-formulary prescriptions could save from $672 to $1008 in co-payments depending on where the prescriptions are filled – domestic mail order or retail.. However, the participant would be required to pay the shipping costs estimated to be $12 per shipment for all drugs ordered.

# Can State employees and retirees obtain safe and effective prescription medications at lower overall cost by purchasing from Canadian pharmacies?

## I. Issue Overview

This analysis addresses the feasibility of enabling participants in the State of Illinois' employee and retiree health benefit programs to purchase a specified set of prescription medications from Canadian vendors.

Importation of prescription medications has become a prominent subject of national interest and debate. Employers, consumers, State and local governments alike are challenging the United States' closed pharmaceutical distribution system, and questioning the Food and Drug Administration's (FDA) position on pharmaceutical importation. The City of Springfield, Massachusetts has implemented a voluntary program encouraging city employees to purchase medicines through a recommended Canadian organization. Minnesota recently announced that it would make vendor recommendations available to citizens that choose to purchase medications from Canadian sources.

Like most employers, the State of Illinois has experienced dramatic increases in pharmacy benefit expenditures for participants in its employee and retiree health benefit programs. And, like any other employer, the State has reviewed its plan design, negotiated with providers for favorable prices, and increased employees' and retirees' cost sharing obligations. In spite of these cost-saving strategies, expenditures for State employees' and retirees' prescription medications have increased approximately 15% each year for the past five years. This trend is expected to continue as technology continues to provide new and better pharmacological solutions to manage acute and chronic illnesses, and as the population ages.

The soaring cost of prescription drugs is not a problem for employers alone. Policy analysts are struggling to find a financially feasible strategy to enable Medicare coverage of prescription medications needed by the nation's elderly, and Medicaid programs in many States are limiting formularies and exploring new purchasing arrangements to lower costs.

Purchasing pharmaceuticals from Canadian sources may provide an important opportunity to reduce costs and extend the purchasing power of employees and retirees to better afford prescription drugs. Favorable exchange rates, Canadian pharmaceutical pricing and distribution practices can make medications needed by employees and retirees available at lower cost to the State than current practice allows.

## II. Research Method and Design

This analysis draws extensively on information gathered through research, by soliciting the views of major organizations and associations within the pharmaceutical industry, and through a fact-finding visit to several of Canada's major pharmaceutical providers arranged by the Office of the Special Advocate for Prescription Drugs. The State of Illinois delegation included:

- Special Advocates for Prescription Drugs, Scott McKibbin and Ram Kamath, Pharm.D.
- Director, Department of Public Health and the State's Chief Medical Officer, Eric Whitaker, M.D., MPH
- Assistant Director. Department of Public Health, Jonathan Dopkeen, Ph.D.
- Pharmacist, Department of Public Health, Ron Gottrich, R.Ph., M.S.
- Legal Counsel, Department of Professional Regulations, Daniel Kelber, JD
- Prosecutor, Department of Professional Regulations, Jay Bogdan, JD, Pharm.D.
- Director of Drug Compliance, Department of Professional Regulations, Yashwant Amin, R.Ph., Ph.D.
- Office of the Governor / DHS, Rachelle Anders, JD, MPH
- Chief Legal counsel, Office of the Governor, Tom Londrigan JD
- Counsel, Office of the Governor, Sheri Klintworth, JD

The delegation met with Canadian government officials, pharmacists and executives from mail-order and Internet pharmacies based in Windsor, Winnipeg and Toronto, including:

- Manitoba Deputy Minister of Health, Milton Sussman; Community and Economic Development Committee of Cabinet, Senior Project Manager, Lea Girman; and, Provincial Health Programs Assistant Deputy Minister, Marcia Thomson; and Manitoba Executive Director, Provincial Drug Programs, Jack Rosentreter.
- CanaRx Medical Director, Peter A. Kuhlmann, M.D; Chief Executive Officer, G. Anthony Howard; and, Vice President of Operations, Mark Matthews B. Sc. Pharm.
- CanAmerica Drugs Inc. Jeremy R. Charney; Symon Honeyborne, International Business Manager; and, Glenn Voth
- CanadaDrugs.Com, Hamza Musaphir, Ph.D., P. Eng., President; Kris Thorkelson, B.Sc. (Pharm), CEO/Chairman; and, Robert Fraser, Director of Pharmacy/Media and Regulatory Relations Officer
- FineLine Solutions, David Rattray, Vice President, Sales and Marketing
- Adv-Care Pharmacy, Amr Bannis, P. Eng., Director; and, Mona Bannis B.Sc. Pharm., Director of Pharmacy

In addition, the analysis incorporates information and analysis provided by organizations that serve pharmaceutical consumers in Illinois, including:

- National Association of Boards of Pharmacy
- Illinois Pharmacists Association
- Illinois Retail Merchants Association
- Members of Illinois State Board of Pharmacy
- Independent Pharmacists
- Deans of University of Illinois Chicago and Midwestern University Colleges of Pharmacy
- Pharmaceutical Research and Manufacturers Association (PhRMA)
- American Association for Retired People (AARP)
- Canadian Pharmacy Providers in Manitoba
- City of Springfield, Massachusetts
- The United States Food and Drug Administration

Acknowledgements, key documents and supporting materials are provided in the Appendices to this report.

The research process was as comprehensive as possible, exploring the following five issue areas.

## A. Consumer Safety

This discussion looks at the many issues surrounding patient safety. It compares procedures for the manufacture, storage and dispensing of pharmaceuticals.

## B. Regulatory Governance

This section compares the regulation and oversight of the Canadian and American pharmaceutical systems and evaluates whether Canada's professional and industry standards are comparable to those of the United States.

## C. Program Drugs

A key factor in examining the feasibility of purchasing pharmaceuticals from Canada concerns the number of medications, the anticipated need for those medications among State of Illinois employees and retirees, and the potential price differential. This section identifies prescription medications most appropriate for consideration, specifically brand name drugs that treat chronic medical conditions.

## D. Projected Cost Savings / Reduction in Benefit Expenditures

This discussion outlines the methodology used to estimate savings, incorporating sensitivity for participation and drug mix.

## E. Policy and Economic Impact

Formal programs to purchase prescription drugs from Canadian pharmacies will likely impact businesses in Illinois. The impact on Illinois' pharmaceutical marketplace and actions of pharmaceutical industry are considered in this section of the analysis.

## III. Research Findings

The following findings reflect the contributions of participants in the multi-agency, interdisciplinary team fact-finding delegation as well as other State of Illinois professional staff.

## A. Consumer Fraud and Safety

**Findings:**

- Employees and retirees can purchase safe and lower cost drugs from Canada.
- Pharmacy practice in Canada is equal or superior to the pharmacy practice in the State of Illinois.
- Several features of the proposed plan designs for State of Illinois employees and retirees could encourage increased patient safety. These design features would include:
    - No "first fill" in the mail order system. Employees and retirees would need to have been prescribed and tolerated a prescription drug for a minimum of one month in the Illinois retail system prior to utilizing the Canadian Mail Order Plan.
    - Patients would be required to submit a detailed medical history
    - Only a restricted list of drugs is available as per the State's formulary for this program.
    - "Unit of Use" packaging sealed and shipped directly from the manufacture to the pharmacy and then to the patient will dramatically cut down patient medication errors and reduce the possibility of counterfeit drugs.
    - The State would develop a Primary Care Pharmacist (PCPh) Model to improve patient safety. Each patient would select a PCPh who would coordinate pharmaceutical care (incorporating prescriptions obtained through local retail pharmacies, domestic mail order pharmacy, and Canadian Mail Order Plan). The State would use a portion of savings generated through the importation program to fund the PCPh Model.

- The Canadian regulatory system provides substantially equivalent protection for the health and safety of the public as is provided for in the State of Illinois. While there are differences in the details of how the pharmacy profession is regulated, the standards of protecting the public health and safety are substantially equivalent.
- Though not identical in statutory or regulatory text, both countries' methods of ensuring safety and efficacy of prescription drugs are comparable.
- Currently the Canadian system for pricing and distribution of pharmaceuticals is less likely than that of the system in the United States to foster drug counterfeiting. Factors include:

- The Canadian system has same price for each drug across different classes of trade (Hospitals, Retail Pharmacies, Government Owned Facilities, Physician Office, Long Term Care Facilities, etc) versus the United States system where the price paid in each class of trade is significantly different.
- In Canada, the secondary market for prescription drugs is limited to small retail transactions between licensed pharmacies.
- Higher retail prices (profits) in the Unite States enable drugs to move through multiple vendors (manufacturer, wholesalers, repackagers, retailer, second repackager, etc), resold and repackaged, potentially several times before reaching the patient.

- The United States and Canada have comparable requirements at virtually every level for the warehousing and storage of pharmaceuticals.

**Discussion:**

The Illinois State Board of Pharmacy, the Ontario College of Pharmacy, and the Manitoba Pharmaceutical Association are all members of the National Association of Boards of Pharmacy (NABP), an independent, international, and impartial association that assists its member boards and jurisdictions in developing, implementing and enforcing uniform standards for the purpose of protecting public health.

### 1. Counterfeit Drugs, Consumer Fraud

The definition of counterfeit drugs is broad and includes those drugs, whether prescription or over-the-counter, that are contaminated, contain inactive or incorrect ingredients, or are otherwise adulterated with more or less active ingredient than is expected. It is estimated that over the past six years, the number of open Food and Drug Administration (FDA) counterfeit drug cases in the United States has more than tripled.[1] The FDA is so concerned with the proliferation of counterfeit drugs that it has launched a Counterfeit Drug Task Force to provide suggestions to reduce the risks posed to the public by counterfeit drugs. The Task Force began its work on July 16, 2003 and is expected to publish the complete findings in January 2004.

The U.S. distribution system typically involves the drug manufacturers distributing their products through wholesalers to the retail or mail order pharmacies. Since many manufacturers ship drugs in large quantities, it is common practice that drugs are repackaged by independent entities, wholesalers, or distribution centers prior to reaching the retailer. The repackaging

[1] *New FDA Initiative to Combat Counterfeit Drugs*, http://www.fda.gov/oc/initiatives/counterfeit/backgrounder.html.

operation is a point of weakness that presents an opportunity for the introduction of counterfeit drugs.[2]

The drug distribution system in Canada appears to be simpler than that of United States. The Canadian government negotiates prices as a part of the approval process. The wholesalers acquire the product at this negotiated price. The product is sold to the retailers at a small premium. The price of the product is essentially same across all classes of trade unlike United States. See Appendix B1

In contrast, the complexity and multiplicity of pricing arrangements in the United States create opportunities for diversion and counterfeiting. In the United States, the cost of a drug varies by the retailer, class of trade, negotiated price, location, etc. The price paid for the same drug by a not-for-profit hospital may be significantly different from the price paid by a retail pharmacy. As a result of the high variability in price, a secondary market has developed that creates situations where a chain of custody cannot be established; buyers may or may not be informed as to the potential lack of integrity of the drugs.

Pharmacy Benefits Managers (PBM) are paying claims for Canadian drugs today, without questioning the medicines' origins or requiring the participant to prove they were actually in Canada (or any other country) when the drug was purchased. This passive posture prevents the employer from enhancing the oversight and safety that accompany an employer sponsored health benefit plan. In addition, the plan participants (employees and retirees) lack the added protections of using health care providers in the employer-contracted network. A similar problem exists for all citizens in Illinois who might wish to obtain lower cost drugs from Canada. Under the current system our most vulnerable citizen (seniors or disabled with chronic health conditions) have no way to tell if the provider at the other end of the internet or toll free number connection is legitimate.

Prescription drugs sold in Canada must be approved by Health Canada's Therapeutic Product Directorate (TPD). Once approved, the TPD issues a Drug Identification Number (DIN) that allows a manufacturer to market the drug in Canada. The DIN is similar to the National Drug Code (NDC) number issued in the United States. Both United States' and Canadian law require pharmaceutical companies to comply with strict Good Manufacturing Practices (GMP).

Many brand name drugs sold in Canada are manufactured in the United States in FDA approved facilities. Based on our first hand observation, Canadian pharmacies dispense sealed containers of medications received from the manufacturer. Other brand drugs that are not manufactured in

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[2] *FDA Counterfeit Drug Task Force Interim Report: Safe and Secure*, U.S. Department of Health and Human Services, Food and Drug Administration, October 2003, page 9.

the United States, are manufactured in facilities approved by Health Canada's Therapeutic Product Directorate (TPD).

### 2. Quality Assurance

Professional associations like the U.S. based IMPAC (Internet and Mail Order Pharmacy Accreditation Commission), NAPAC (North American Pharmacy Accreditation Commission), CIPA (Canadian International Pharmacy Association), and MIPA (Manitoba International Pharmacist Association) provide tools for monitoring and quality assurance to individual Canadian pharmacies. Mechanisms are in place to assure the quality of pharmaceutical dispensing and distribution, such as:

- Confirming competency and appropriate licensing of the provider, technicians and the pharmacists
- Performance improvement processes
- Monitoring dispensing error

### 3. Monitoring

The Canadian pharmacy system has both internal and external monitoring systems in place. The pharmacist in charge is required to maintain, monitor, and supervise staff and their professional practices. The pharmacist also ensures that the pharmacy is operating in complete compliance with the provincial laws.

Provincial agency inspectors conduct regular inspections of pharmacies. Review of the inspectors' scope of inspection indicates that they function under a set of standards that appear to be as strict as those maintained by the Office of Drug Compliance in the State of Illinois. The State of Illinois' pharmacists participating in the fact-finding delegation observed that incident reporting of internal process errors was more rigorous in Canadian provinces of Manitoba and Ontario than in the United States.

### 4. Drug Dispensing

All processes, from manufacturing to final consumer consumption, impact product safety. All pharmacies visited by the team provided evidence of their adherence to quality control measures throughout their processes, i.e. procurement, dispensing and counseling. The quality control measures and inspections by the provincial authorities are designed to enhance safety.

Pharmacies visited by the team used similar processes to fill prescriptions. The patients from United States are required to register with the pharmacy, providing them with brief medical

history, including allergies, medication history, and diagnoses. The registration process creates an electronic patient profile. Prescriptions mailed or faxed by the patients are entered in the patient profile by a pharmacy technician. The computer system is designed to identify and trigger warnings on potential drug therapy problems including: drug-drug interactions, drug-allergy checks, under/over dose. A registered pharmacist then reviews the record and if the pharmacist has any questions, either the patient or the patient's physician is contacted for clarification. If prescription is deemed appropriate and consistent with the patient's medical history, it is then passed on to a Canadian licensed physician for approval and rewriting. Canadian law requires that all prescriptions filled by Canadian pharmacists have to be written by a physician licensed in Canada. The Canadian licensed physician reviews the prescription and if satisfied with the appropriateness, rewrites the prescription and passes it on to the fulfillment area of the pharmacy. It was noted that some pharmacies reimburse the Canadian licensed physicians by the number of prescriptions reviewed and not by the number approved and rewritten.

In the fulfillment area, a pharmacy technician prepares the order and it is checked by a registered pharmacist. Bar code technology is extensively used during this phase to achieve high degree of accuracy. The quantities dispensed are in manufacturer supplied units. The medication containers are not opened by the pharmacist or the technician during the process. It was noted that the pharmacist had all documentation – the original prescription, computer generated warnings (if any), and the prescription rewritten by the Canadian licensed physician available at the time of final check. It is then passed on to the shipping area where it is packed per industry standards and shipped to the patient.

### 5. Warehousing and Storage

The United States and Canada have comparable requirements at virtually every level for warehousing and storage of pharmaceuticals. Both require quality control units to test and inspect the product and its packaging; segregation of untested, tested and approved or rejected pharmaceuticals; and, that raw materials be tested before production and the finished product be tested after production and in subsequent distribution. Labeling requirements are substantially similar and labeling contains directions for storing the pharmaceutical under appropriate conditions of temperature, humidity, and light. The two countries have similar building design and construction features comparable requirements for production and storage, and extensive record keeping requirements. See Appendix A-2.

### 6. Consumer Counseling and Education

The Manitoba and Ontario Standards of Pharmacy Practice require that the pharmacist, using unique knowledge and skills, shall promote safe and effective use of medication by educating

patients about their drug therapy. The pharmacist is required to document the occurrence of drug consultation, and this document becomes the permanent record in the patient profile.
The Canadian Pharmacy Association provides individual establishments with tools to evaluate performance quality by determination of consumer satisfaction. All consumer complaints are also evaluated by the provincial agencies. A detailed record of the complaint and follow-up is maintained, much like the practice in the State of Illinois.

## B. Regulatory Governance

### 1. Professional Education and Practice

**Findings:**

The educational requirements and professional regulation of pharmacists' in the Canadian provinces of Ontario and Manitoba are as rigorous as those of Illinois.

**Discussion:**

Each Canadian province regulates the practice of pharmacy in that province; Canada's federal government regulates drug safety. This is precisely how such regulation occurs in the United States. The fact-finding team visited pharmacies in Ontario and Manitoba. These provinces are used as the basis for the following comparison.

The Illinois Pharmacy Practice Act of 1987 (225 ILCS 85/1, *et seq.*) and the Rules for its Administration (Ill. Admin. Code tit. 68, § 1330) were established to ensure the safety of patients who require prescription medication. The Illinois Department of Professional Regulation (IDPR) regulates the pharmacy profession in Illinois. Professional boards advise the IDPR. The Board of Pharmacy consists of seven licensed pharmacists and two public members who are not related to the profession of pharmacy in any way, each appointed by the Governor. The Department is divided into various divisions that oversee regulatory functions. There is licensing and testing, complaint intake, investigations, and prosecutions. All issues ending with a denial of an application or discipline have a right to a hearing within the Department, and a right to further appeal with the courts.

The Board reviews all applications for licensure, participates in the disciplinary proceedings against registrants, and advises the Department when called upon their expertise. While great deference is given to the Board of Pharmacy, by statute, it is only permitted to make recommendations to the Director of the Department, who is sanctioned as the final decision maker for the Department. When the Director disagrees with the Board's recommendation, s/he need only inform the Board of the decision to overturn the Board's recommendation. The Board

has no recourse beyond the Director. This structure ensures that the profession does not have the last word in the regulation of the profession. Rather it is the Department, acting as a disinterested party that plays that role.

In Ontario and Manitoba the pharmacy profession is largely self-regulated. Ontario's regulatory body is the Ontario College of Pharmacy; Manitoba's is the Manitoba Pharmaceutical Association (but may soon change its name to the Manitoba College of Pharmacy). Both agencies are organized similarly, and so are treated here together. All registered pharmacists are members of the College and Association. Members vote to elect a Council that has the authority to enforce the regulatory law for each province. While the College and Association fall loosely under the authority of the Ministry of Health for each province, by and large they operate independently. The Councils appoint committees for registration and licensing, complaint intake, investigations, etc. There is a right to hearing within the College and Association, and a right to further appeal in the courts.

There are substantial similarities between the Illinois education requirements and that of the two Canadian provinces visited. Illinois requires a five-year degree in pharmacy whereas Ontario and Manitoba only require a four-year degree in pharmacy. Approved programs in Illinois require a 400-hour internship as part of the five-year degree. In Manitoba the internship must be 360 hours after completion of the four-year degree. And in Ontario a 12-16 week internship is required after the completion of a four-year degree. The examinations required by Illinois and the Canadian provinces are substantially equivalent in regard to standards of practice and care. They differ only as to the jurisdictional examinations as they test State and federal law in Illinois, and provincial and federal law in Ontario and Manitoba. Given the similar subject matter covered by these examinations, it is fair to say that the extra year of college required in Illinois does not preclude the Canadian pharmacy students from having to learn a substantially equivalent amount of information.

In Illinois an applicant for Pharmacist licensure must be a graduate of a both a professional degree program in pharmacy and a program of at least five academic years of post-secondary education at an accredited university. All American Council on Pharmaceutical Education (ACPE) approved programs are acceptable. If a candidate has attended a five year first professional degree pharmacy program that has not been approved, then s/he must go through an approved course of clinical study. After IDPR accepts a candidate's education, s/he must pass, a licensure examination consisting of theoretical and applied pharmaceutical sciences and pharmaceutical jurisprudence.

In Ontario a candidate for licensure must be a graduate from the Faculty of Pharmacy, University of Toronto or a comparable academic program accredited by Canadian Council for Accreditation of Pharmacy Programs (CCAP) or American Council on Pharmaceutical Education (ACPE). If a

candidate has not graduated from an approved program, the candidate will have to pass a separate document evaluation and examination given by the Pharmacy Examining Board of Canada (PEBC) prior to sitting for the licensing (qualifying) examination. The approved programs are four year degree programs. Candidates from approved programs must attend a Structured Practical Training (SPT) studentship for their last semester of school (16 weeks) where they work under the supervision of a licensed pharmacist in a community or hospital licensed pharmacy. After graduating from an approved program, the candidate must complete a 12 week SPT internship for more advanced practical training under a licensed pharmacist. Candidates from non-approved programs must complete a 16 week SPT internship. Upon completion of the educational requirements, the candidate must pass the evaluating examination given by the PEBC and the Jurisprudence Examination given by the Ontario College of Pharmacists (their regulatory body).

A candidate for licensure as a pharmacist in Manitoba must hold a degree from a college, school or faculty of pharmacy approved by the council of the association (Manitoba Pharmaceutical Association – their regulatory body), or the candidate must hold a degree from a program that the PEBC has determined is substantially equivalent to the afore mentioned approved degree. There is no mention in the regulations as to what the length of the pharmacy program must be. However, all Canadian schools of pharmacy are four-year programs. The examinations that must be passed are the same as those required by Ontario other than the jurisprudence examination. After completion of the examination(s) required by the PEBC, the candidate must complete a 360 hour supervised internship program served in a licensed pharmacy under the supervision of a licensed pharmacist approved as a preceptor by the Council.

## 2. Industry Regulation

Findings:

The manufacturing, storage, and distribution practices required by Canadian law appear to be as rigorous as those governing the practices of pharmacies in Illinois and in the United States generally.

Discussion:

The pharmacy industry in Canada is regulated much like that of the United States. Both countries have policies that require before any drugs are approved and distributed for use in general medicine, they must first be proven to be safe and effective through clinical studies. Second, all drugs sold in Canada must be manufactured according to strict quality standards in facilities approved by Health Canada. Focus on the manufacturing, storage and distribution process is addressed in Appendix A-1.

## C. Projected Program Drugs

A list of brand name prescription medications appropriate for long term use was developed based on the current pharmaceutical use by State benefit participants as reported by the State's PBM. Classes of medications, such as controlled substances, antimicrobials, all generics and medications requiring special storage or handling procedures, or medications otherwise deemed unsuitable for importation were not considered for inclusion. The list under consideration is provided in Appendix A-2

## D. Projected Cost Savings / Reduction in Benefit Expenditures

Findings:

Allowing the state employees and retirees to obtain a defined set of brand name maintenance medications used in the treatment of chronic conditions from Canada has the potential to save the State a substantial expense. However, how much the State saves depends on several factors. See Appendix A-3.

Discussion:

The total potential savings if all eligible prescriptions for program drugs employees and retirees are filled through Canadian pharmacies is estimated at $90.7 million per year. Multiple factors will influence the magnitude of savings. They include the currency exchange rate, drug price increases, level of participation and implementation and operational costs.

The currency exchange rate has major impact on the cost differential between United States and Canadian prices. During the past year the Canadian dollar has steadily risen in relations to the. US dollar, reducing the savings for US consumers importing drugs from Canada.

The negotiated price for each of the eligible drugs (formulary) must be less than the price available in U.S. A specific drug could be removed from or added to the State's Canadian program based on cost and any potential price changes.

At present, the prescription drug benefit provided to the employees and retirees in the Managed Care Plans are considered "carved-in". Our recommendation assumes these drug benefits would be "carved-out" of the Managed Care Plans and consolidated with the drug spend under the QCHP Plan. For this to occur, CMS would need to negotiate with seven different Managed Care Plan vendors for the appropriate premium reduction for the reduced drug risk. The State would

also likely want to engage an outside actuary to verify the Managed Care Plan providers proposed rate reductions.

This negotiation process could take several weeks to complete and could be slowed by approvals needed from the Illinois Department of Insurance for changes to filed insurance plans and rates.

The table below illustrates the potential co-payment savings to employees and retirees under the proposed Canadian Mail Order Plan

| | Quality Care Health Plan Administered by Caremark, Inc. | | Managed Care Plans | |
|---|---|---|---|---|
| | Formulary Brand Drugs | Non-formulary Drugs | Formulary Brand Drugs | Non-formulary Brand Drugs |
| Annual co-payment for three prescriptions at retail | $504 | $1008 | $180 | $360 |
| Annual co-payment for three prescriptions through domestic mail order (2 co-payments for 3 months supply) | $336 | $672 | $120 | $240 |

The level of employee and retiree participation would also affect the amount saved. Plan design that waives the copayment and makes the employee responsible for paying only the shipping cost is expected to be most attractive. The current Caremark formulary brand co-payment is $14 per month and non-formulary brand is $28 per month. Co-payments for a three-month supply of a prescription at retail are $42 and $84, and at mail order are $28 and $56 respectively. If an individual gets three non-formulary brand prescriptions through the Canadian Mail Order Plan, they could save up to $1008 per year in co-payments. The shipping cost per order is expected to be $12 dollars per shipment. This may encourage the participants to consolidate multiple prescriptions in only one order per quarter.

## E. Policy and Economic Impact

Findings:

The state employees' and retirees' prescription drug benefit plan and the plan participants will achieve cost savings by procuring medications from Canada.

A formal program to purchase prescription drugs from Canadian pharmacies is likely to impact retail pharmacies in Illinois. This impact can be minimized and patient safety enhanced by implementing a Primary Care Pharmacist Model. See Appendix A-4.

Discussion:

Impact on Illinois' pharmaceutical marketplace and actions of the pharmaceutical industry are considered in this section of the analysis.

Under the proposed plan, Illinois retail pharmacies will lose prescriptions to Canadian pharmacies. According to the Illinois Retail Merchants Association (IRMA), this may result in reduction of store hours and smaller number of local jobs. IRMA was asked to provide supporting documentation for this claim during the meeting on September 26, 2003 that as of the date of this report has not been received. At present there is high a demand for pharmacists in Illinois, and it is likely that they would find employment in other sectors such as hospital pharmacy and long-term care pharmacies. Publicly traded drug store chains such as Illinois based Walgreen continue to report new store openings at a record pace, and increased revenues and profits. Walgreen October 2, 2003 press release[3] highlighted the following company facts:

- September sales of $2,795,900,000, an increase of 17.6 percent from $2,376,495,000 for the same month in 2002
- Sales in comparable stores (those open at least a year) rose 12.9 percent
- September pharmacy sales increased 20.8 percent, while comparable pharmacy sales rose 16.9 percent
- Total prescriptions filled at comparable stores increased 10.0 percent
- Calendar year-to-date sales were $24,645,592,000, an increase of 13.6 percent from $21,703,210,000 in 2002
- At Sept. 30 the company operated 4,229 drugstores in 44 states and Puerto Rico, versus 3,888 a year ago

[3] http://money.cnn.com/services/tickerheadlines/prn/cgth010.P1.10012003183837.29659.htm

Based on comments in Walgreen 8K/A filed with the Securities and Exchange Commission on September 29, 2003[4], Walgreen CEO Mr. Bernauer made the following observations: "We had a strong fourth quarter, as non-pharmacy sales bounced back," said Bernauer. "We also opened a record 127 new stores in August alone, and our store opening program is on track to reach 7,000 stores by 2010."

The PCPh program (see appendix A-4) would offset the increasing local revenue shift to domestic mail order and the proposed non-domestic mail order program by paying the pharmacists to manage the drug therapy of participating employees and retirees.

The loss of sales and resulting loss in sales tax revenue may impact State and local government budgets. Additional data and analysis is required to fully explore this dimension. But, given that employees/retirees are expected to see a significant portion of the program savings, the total impact for a local community is likely to be positive because the money saved is likely to go back into the community.

The volume of drugs Canadian pharmacies can purchase from Canadian wholesalers is another consideration. Several Canadian pharmacies currently shipping medication to U.S. consumers have received warnings from the pharmaceutical manufacturers that they will stop shipments unless the pharmacies discontinue. Based on our fact finding teams first hand observations and discussion with the Manitoba provincial government and pharmacy providers, we do not feel the manufacturers rhetoric to restrict supply will ever materialize either broadly or consistently, and not at all in the Canadian pharmacies that are hybrid – internet and retail for two reasons. First limiting supply to Canadians pharmacies may risk their Canadian patent protection; second, as the Minnesota Attorney General and Illinois Attorney General are currently investigating any concerted effort by the pharmaceutical companies to limit supply may violate US antitrust laws. Additionally, since the use of Canadian pharmacies would be voluntary, Illinois consumers always have alternative sources of medication in the U.S.

Actions taken by the pharmaceutical industry and associated businesses in response to State action to encourage the purchase of Canadian pharmaceuticals by State employees and retirees could have a financial impact on State revenues and expenses.

Pharmaceutical manufacturers have the option of canceling the OBRA 90 agreement with U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services (CMMS). The Omnibus Budget Reconciliation Act of 1990 provides that Medicaid will cover a drug only after the pharmaceutical manufacturer of that drug has entered in to an agreement with CMMS, where by the pharmaceutical manufacturer agrees to provide rebates to each of the states

[4] http://www.sec.gov/Archives/edgar/data/104207/000010420703000010/0000104207-03-000010.txt

for drugs covered by Medicaid. Therefore, if a manufacturer cancelled the agreement with CMMS, the manufacturer would no longer receive payments for Medicaid drugs in any state, which translates into an estimated $30 billion loss. If a manufacturer did opt out, a greater impact would be felt by the consumers, since those drugs would not be covered by Medicaid. The State could decide to continue to cover those drugs at the expense of the State and forgo federal match and rebates, in which case the impact on the State could be quite significant. However, the pharmaceutical manufacturers are not likely to cancel these agreements in light of the potential collective loss of up to $30 billion in sales.

In retaliation for the State's actions, pharmaceutical manufacturers could cancel supplemental rebate contracts with the Illinois Department of Public Aid (IDPA). If all manufacturers that have contracts with IDPA cancel, the annual financial impact to the State would be approximately $50 million. However, the manufacturers have gained market advantage by way of the supplemental rebate agreements, which they would forgo if they cancelled. If not all manufacturers cancelled, those that did would be at a disadvantage among the other manufacturers. IDPA expects to receive $400 million in OBRA 90 and supplemental rebates during FY03, amounting to 25% of the budget.

The pharmaceutical manufacturers could also cancel the rebate agreements with the State's PBM. However, rebate agreements between the manufacturers and the PBMs are not likely to be exclusive to the State business, so canceling those contracts may hurt both other payors and the manufacturers in a broader market.

In summary, although the pharmaceutical manufacturers may threaten to take any of the above retaliatory actions, we do not believe they will do so.

# IV. Options Analysis

Criteria were developed for the purposes of evaluating each of the alternatives that emerged from the research and analysis. The alternatives would be assessed along these criteria in order to arrive at a policy recommendation that optimized the best overall course to achieve the central objective of the study: Which of the developed design options would best enable the State's employees and retirees to purchase prescription drugs safely through Canadian internet and mail-order pharmacies, lowering the overall cost to the State and its health plan enrollees?

The criteria fall broadly into four categories: effectiveness, cost, feasibility and timing

- Effectiveness criteria would be measures of how well the option meets the plan members' needs for filling their prescriptions safely and correctly. Greater assurance of safety and accuracy is desired.

- Cost criteria would include measures of savings (for the individual as well as the State) and measures of costs (of both implementation and administration). Greater savings and lower costs are both desirable.

- Feasibility criteria enable independent assessment of the factors that might impede the likelihood of success. These measures include relative assessment of factors such as implementation difficulty (ease is desired), regulatory impediments (fewer are better), and political difficulty (less opposition and greater likelihood of broad-based support are preferred).

- Timing criteria enable assessment of the relative (or even precise) time to implementation and time to achieved savings. Shorter time frames for both implementation and to achieving savings are preferred.

The criteria are necessary to the option evaluation because none of the possible options will perform well under all criteria. Higher assurance of safety (effectiveness) may come at higher administrative expense (costs). However, maximum savings might be achieved by an option that has the highest administrative costs and the highest assurance of patient safety (effectiveness). Priority is given to the key elements of ensuring patient safety (effectiveness) and being implementable (feasibility) while lowering overall costs (costs). Consequently, an option that does not ensure patient safety would not be acceptable under any circumstances, and neither would options that are either impossible to implement or which achieve too little savings.

The table on the next page details the category, criteria and preferred direction of measure used to develop the plan design options.

| Category | Criteria | Preferred Direction of Measure |
|---|---|---|
| Effectiveness | Assures safety of the product | Closed versus open system |
| | Assures prescription accuracy and correctness of product dispensed | Completeness of process steps |
| | Continuity of supply (reliability for patient) | No possible supply interruptions |
| | Availability of qualified patient counseling | Steps and quality of patient interactions |
| | Enrollment / Participation | Shorter enrollment process with highest participation |
| Feasibility | Implementation | Ease of overall implementation |
| | Operation | Ability to handle all eligible prescriptions |
| | Did regulatory impediments exist and could changes be likely enacted | No changes needed. If changes were required, high probability for approval |
| | Political ease or difficulty | Ease versus difficult |
| | Enrollment / Participation | Highest versus lowest |
| | Likelihood of manufacture retaliation | Lowest versus highest |
| Cost | Costs/Savings per transaction | Lowest cost and highest savings |
| | Costs/Savings aggregate | Highest savings taking participation into account |
| Time | How long to implement option | Difficulty and number of contract steps |
| | Time needed for option to achieve savings | Speed for savings to accrue to participant and State |
| | Time needed to overcome any regulatory impediments and changes | No changes needed is preferred |

## Options

Based on the multi-agency, interdisciplinary teamwork, five discrete options were developed for review. These options build in structure, control and savings for the State and the employees and retirees.

### 1. Voluntary purchasing and reimbursement (no incentive)

This alternative involves no active participation by the State. Plan participants could voluntarily purchase medication from a Canadian pharmacy and submit a claim for reimbursement from their PBM; the PBM would reimburse the cost minus eligible co-payment.

This option provides no additional safeguards to ensure quality control or patient safety. Because the State would be only a passive participant in this model, the State would not direct participants to purchase from particular Canadian pharmacies. Thus, the State could not ensure that participants would purchase drugs from Canadian pharmacies with high quality safeguards.

In terms of cost to the State, the savings per transaction would not be predictable; the aggregate savings may not be significant because not all drugs are cheaper in Canada, and because the exchange rate per transaction is not constant. Because the benefit plan will reimburse the purchase of any covered drug, prescriptions would be paid that may not be filled under subsequent options because of a drug's non-availability due to unfavorable cost. The cost of implementation and operation would be minimal.

The time-line is short and most favorable; the development/implementation would be rapid, considering that it may only entail publicizing and educating the consumer on the use of Canadian pharmacies. The savings, if any, would be recognized almost immediately.

### 2. Voluntary purchasing and reimbursement with an incentive

This option requires a minor change in the current benefit design, which would reduce employees' and retiree' out-of-pocket costs to encourage use of Canadian pharmacies. The incentive would be a discounted co-payment, or no co-payment at all.

Under this model, the State would provide several quality control assurances to protect plan participants. Specifically, the State would vet Canadian pharmacies and allow participants to use only those pharmacies that are approved, and provide quality products and services. By providing incentives to State employees to use Canadian pharmacies and by incorporating

quality control safeguards, the State will likely increase participation. This option offers a higher level of safety compared to Option 1.

The cost considerations improve when employees have financial incentives. Since participation will likely increase, the savings will increase overall. The implementation and operating costs will increase because of the necessity of creating and maintaining concrete relationships with certain Canadian pharmacies.

The time needed to implement increases because more time is necessary to develop and implement the program that the incentive supports. Consequently, the time before savings also increases.

**3. Voluntary purchasing, in which the State publishes reimbursement rates, lists eligible prescriptions and eligible pharmacies**

This alternative would entail a voluntary program for State retirees and employees in which the reimbursement rates for a specified list of eligible prescription drugs are available from certain eligible Canadian pharmacies.

Under this option, the State would control which drugs would be eligible for reimbursement. This would allow the State to limit the list of drugs to those that could be safely and cost-effectively purchased from eligible Canadian pharmacies. As described in the prior model, this model would also involve the State's vetting of Canadian pharmacies to ensure that the participating pharmacies meet the State's standards for safety.

This option would allow the State to maintain relationships with pharmacies that offer reliable products and service. The State could impose operational requirements on all participating pharmacies; for example, the State may require that the pharmacies provide a 24 hour customer service call center and that a pharmacist is on-call at all times.

In terms of costs, this option would provide greater savings per transaction because the list of eligible prescriptions would include only those that are less expensive than the same drug sold in the U.S. The cost associated with educating employees on the availability of the option would be slightly higher than the prior option. The cost of vetting eligible pharmacies would continue, and there may be additional staff costs in maintaining and publishing the program formulary and costs.

A moderate amount of time is required prior to the development and implementation of this option. It is necessary to create a list of approved medications, establish the pricing, and inspect and choose eligible pharmacies.

**4. Voluntary, engage a non-domestic PBM model, with an incentive (Springfield, MA model)**

This option is identical to the program in place in Springfield, Massachusetts. It involves a voluntary, incentive-based program in which the State would engage a non-domestic Pharmacy Benefits Manager (PBM) to facilitate the purchase of eligible Canadian prescriptions by state employees and retirees. The incentive may come in the form of partial or total forgiveness of the co-payment. The State would not contract directly with the PBM, but rather the PBM would submit a periodic invoice to the State, indicating the number of prescriptions filled for state employees and retirees in the previous billing period. As part of registration, the employee would authorize the State to pay the PBM for prescriptions obtained from eligible Canadian pharmacies.

This option offers the same quality control safeguards as described in the previous option; the State would be able to restrict the eligible drugs to those that could be safely and cost-effectively distributed by Canadian pharmacies. The level of participation will increase with this option because a PBM would allow the consumer the convenience of having one entity with which to communicate.

This model offers potentially higher savings per transaction because the PBM would offer a fixed shipping cost. Aggregate savings would be greater because the PBM entity will deliver a constant price across all pharmacies. Administrative costs would be lower because the State would consolidate billing through a single source. The implementation and operation costs could potentially be high due to the cost associated with choosing a PBM that can handle the potential volume, inspecting the pharmacies used by the PBM, and reviewing documentation of the sources of the drugs.

This option could be developed and implemented in a reasonable amount of time, but would depend on the ability of an existing or start-up PBM to handle the potential volume associated with the Illinois plan.

**5. Voluntary, engage a non-domestic PBM model, with incentive via contract**

This option is very similar to the previous model except the State would enter into a contract with the PBM.

The safety considerations are the same as presented in the previous option; the quality of the product and accuracy would be contractually required to remain consistent. The reliability of the product increases with this option because the contract can specify that the PBM guarantee that

the pharmacies it uses purchase their products from specific wholesalers who provide quality drugs.

This option delivers the maximum projected savings. In terms of costs, the savings per transaction is predicted to be high, given the contracted cost with the PBM; the PBM and the State would have negotiated the rates of the drugs in order for the option to be financially feasible. The aggregate costs would also be low, based on the contracted fees and costs. In this option, the State has full knowledge of the aggregate savings it will realize.

Based on this knowledge of the projected savings, this option (#5) becomes the only alternative under which the proposed Primary Care Pharmacist Model (see AppendixA-4) becomes feasible. This program would make available a local pharmacist to consult on *all* prescriptions the employee or retiree may be using.

Because of the nature of contract negotiations, the time for development and implementation will be greater than the options previously discussed

# V. Summary

Based on the foregoing review, the Office of the Special Advocates for Prescription Drugs finds that it is feasible to implement a pharmaceutical purchasing program allowing active and retired members of State of Illinois health benefit plans to import specified medications from qualified Canadian pharmacies, and that purchasing specified medications from qualified Canadian pharmacies promises significant cost savings to the State without jeopardizing public safety.

**Recommendation:**

Select the plan design option (Option #5) that provides for the maximum safety, participation and savings. This would be the option in which the State contracts with a non-domestic PBM, sets up the Primary Care Pharmacist Model, and requires the employees and retirees to pay only the shipping cost for the drugs. (This is a benefit incentive, with no prescription co-payment for Canadian-ordered drugs).

Recommend that the Governor direct the department of Central Management Services (CMS) and the Office of the Special Advocate for Prescription Drugs (OSAPD) to contract with a vendor as soon as practicable and target implementation of Caremark enrollment under the Quality Care Health Plan (QCHP) on April 1, 2004 for a limited number of drugs (more restricted than the recommended list of drugs for this program detailed in Appendix A-2). The complete list of drugs for this program is recommended to be available on July 1, 2004.

To enhance patient safety, we further recommend an ingredient and quality assurance-testing program be implemented. The State would work with Illinois Department of Public Health and the University of Illinois (UIC) Chicago College of Pharmacy to test drugs to ensure quality of both the domestic and non-domestic drug supply purchased by employees and retirees.

# Appendices

The Appendices present an effort to display the full range of materials that were assembled and brought forth to the Task Group, led by the Special Advocates for Prescription Drugs, and bear directly upon the effort to assess the feasibility of having State employees and retirees, and their covered dependents, purchase prescription drugs safely and cost-effectively.

The materials appended are organized broadly into several categories. These are:

A. **Expanded explanation of topics summarized in the main report.**
B. **Task Group Documentation**
C. **Independent governmental research (e.g., US Congressional Research Service)**
D. **Correspondence and materials regarding that support the feasibility of the utilizing the Canadian internet pharmacy industry**
E. **Correspondence against utilizing the Canadian internet pharmacy industry**
F. **Materials opposing the use of Canadian internet pharmacies**

| App. | Source | Description | Details |
|---|---|---|---|
| **A** | **Expanded explanation of topics summarized in the main report** | | |
| 1. | IDPH Division of Food, Drugs and Dairies | Comparative Analysis of U.S. and Canadian Regulatory Requirements Regarding the Warehousing and Storage of Pharmaceuticals | |
| 2. | Caremark, State of Illinois Data | Potential formulary | Based on current medication use |
| 3. | Special Advocates, CMS | Cost-estimation methodology | Also addresses Managed Care Plans |
| 4. | Special Advocates, CMS | Primary Care Pharmacist (PCPh) Model | PCPh concept and implementation |
| | | | |
| **B** | **Task group documentation** | | |
| 1. | Pharmacy Section, IDPR Director and Prosecutor, | Comparative analysis of pharmacy practice in Illinois and Canadian provicnces of Manitoba and Ontario | |

| | | | |
|---|---|---|---|
| | Office of Pharmacy Compliance | | |
| A. | Visited Canadian Pharmacies | Sample pharmaceutical invoices | |
| B. | Canadian regulatory bodies and Canadian | Regulatory correspondence, survey forms, policies and procedures forms from and between | |

| App. | Source | Description | Details |
|---|---|---|---|
| C. | Visited Canadian Pharmacies | Notice of U.S. Food & Drug Administration Action, Florida District Office | Notification of shipment being held |
| D. | Visited Canadian Pharmacies | Sample prescription refill form | |
| E. | Visited Canadian Pharmacies | Sample patient history profiles and requisite patient forms | |
| F. | Visited Canadian Pharmacies | Sample pharmacist checklists, prescription samples and verbal order forms | |
| G. | Visited Canadian Pharmacies | Sample patient counseling guidelines, tracking and drug utilization review and interaction advisories | |
| H. | Visited Canadian Pharmacies | Sample data on Medication incident reports, protocols for dispensing errors, sample error data and logs, | |
| I. | Visited Canadian Pharmacies | Sample pre and post-checklists on therapeutic screenings | |
| J. | Visited Canadian Pharmacies | Pharmacist- MD Checklist sample interaction tracking and summary | |
| K. | Visited Canadian Pharmacies | Sample Internet pharmacy ordering and release forms | |
| | | | |
| **C** | **Governmental reports and documents** | | |
| 1. | Congressional Research Service | Memorandum Re: Questions Concerning the U.S. and Canadian Regulatory Systems for Approving and Distributing Prescription Drugs, May 28, 2003 | Substantive and detailed assessment of comparability between U.S. and Canadian regulation |
| 2. | U.S. Food & Drug Administration | Agreement of Cooperation Between the Canadian Department of National Health and Welfare and the Food & Drug Administration | Long standing agreement recognizing mutual capabilities |

| App. | Source | Description | Details |
|---|---|---|---|
| 3. | Patented Medicine Prices Review Board (Canada) | 2002 Annual Report of the Patented Medicine Prices Review Board to the House of Commons (Ontario, Canada May 30, 2003) | |
| 4. | Ministry of Health, Manitoba, Canada | Proposed Agreement by Manitoba Pharmacists Concerning Delivery Services To The Rest Of Canada And To The United States | Document re: standards & controls on all North American services |
| 5. | U.S. Food & Drug Administration | U.S. Food & Drug Administration notice of counterfeit Lipitor and recall in the U.S. market | Evidence of US problems not encountered in Canada |
| | | | |
| **D.** | **Correspondence regarding that support the feasibility of the utilizing the Canadian internet pharmacy industry** | | |
| 1. | Dean, Chicago College of Pharmacy | Letter of Support | Support for program concepts |
| 2. | Dean, College of Pharmacy, UIC | Letter of Support | Concept support but reservations re: economic effect and legality |
| 3. | Executive Director, National Association of Boards of Pharmacy (headquartered in Illinois) | Letter of Support | Support conditioned on legislative changes re: legality and Primary Care Pharmacist proposal in Code, with standards ensuring patient safety |
| 4. | Medical Director, Dreyer Medical Clinic, Aurora, Illinois | Letter of Support | Not encountered any quality or safety problems with Canadian drugs imported by patients. |
| | | | |

| App. | Source | Description | Details |
|---|---|---|---|
| **E.** | **Correspondence against utilizing the Canadian internet pharmacy industry** | | |
| 1. | President, Illinois Pharmacists Association | Letter | Expressed concern over patient safety |
| 2. | Acting Executive Director, Illinois Pharmacists Association | Letter | Concerns of patient safety, and supplanting of pharmacist role as advisor |

## Appendix A-1

# Comparative Analysis of U.S. and Canadian Regulatory Requirements Regarding the Warehousing and Storage of Pharmaceuticals

### Summary

This memorandum is limited to a comparative analysis of U.S. and Canadian regulatory requirements regarding the warehousing and storage of pharmaceuticals which are manufactured in the U.S., have U.S./F.D.A. approval and are to be reimported into the U.S. from Canada. It will not deal with drug formulation, manufacture, or initial U.S./F.D.A. authorization. Selected provisions from the Good Manufacturing Practices of both Canadian and U.S. regulatory requirements were chosen in the preparation of this analysis. The Good Manufacturing Practices of both countries were chosen because they apply not just to the manufacturers of pharmaceuticals, but to virtually every entity which manufactures, processes, packs, holds or distributes pharmaceuticals.

The Canadian provisions are found under Food and Drug Regulations, Part C Drugs, Division 2 Good Manufacturing Practices (***Exhibit A attached***) and the U.S. provisions are found under Code of Federal Regulations (CFR) Title 21–Food and Drugs, Chapter I–Food and Drug Administration Department of Health and Human Services, Part 211–Current Good Manufacturing Practice for Finished Pharmaceuticals (***Exhibit B attached***).

As can be seen from the analysis of the selected U.S. and Canadian pharmaceutical regulatory provisions, the two countries have comparable requirements at virtually every level for the Warehousing and Storage of Pharmaceuticals.

## INITIAL PROBLEM

There is a threshold hurdle for the reimportation of pharmaceuticals that will be difficult to overcome. Drugs are approved for use in the U.S. pursuant to the provisions of 21 U.S.C. § 355 [New Drugs], which requires among other things submission to the Secretary as a part of the application: (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug. 21 U.S.C. § 381 [Imports and exports] subsection (d)(1) deals with reimportation, and states: "*Except as provided in paragraph (2) and section 384 of this title, no drug subject to section 353(b) of this title or composed wholly or partly of insulin which is manufactured in a State and exported may be imported into the United States unless the drug is imported by the manufacturer of the drug.*" 21 U.S.C. § 331 [Prohibited acts] subsection (t) prohibits in relevant part "*The importation of a drug in violation of section 381(d)(1) of this title . . . .*" Notwithstanding this general prohibition, 21 U.S.C. § 384 [Importation of covered products] (supra) allows the Secretary to promulgate regulations permitting pharmacists and wholesalers to import into the United States covered products. However, procedural requirements associated with this statutory exemption are virtually as lengthy as new drug approval and, in any event, the Secretary has not promulgated such regulations.

The rationale for U.S./F.D.A.'s prohibition goes back a number of years and has most recently been restated in a Warning Letter to CanaRx Services, Inc. dated September 16, 2003, wherein U.S./F.D.A. stated in relevant part "Frequently, drugs sold outside of the U.S. are not manufactured by a firm that has FDA approval for that drug. Moreover, ***even if the manufacturer has FDA approval for a drug, the version produced for foreign markets usually does not meet all of the requirements of the U.S. approval, and thus it is considered to be unapproved.*** 21 U.S.C. 355." (Emphasis added)

Succinctly stated, a drug manufactured in the U.S., with US./F.D.A. approval, for the U.S. market may be formulated differently for foreign markets. Therefore, it would be an unapproved drug for reimportation, except for reimportation by the manufacturer, unless the requirements of 21 U.S.C. § 384 [Importation of covered products] can be met.

## BUILDING REQUIREMENT

The U.S. and Canada both have regulations for the premises/building where pharmaceuticals are to be manufactured, processed, packed, or held, which require that they be maintained in a clean and sanitary condition. The Canadian provisions are found at C.02.004. The U.S. provisions are found at 21 CFR Sec. 211.42, 21 CFR Sec. 211.46, 21 CFR Sec. 211.56. Both countries have comparable requirements with regard to design and construction features, ventilation, air filtration, heating, cooling and sanitation. These requirements include proper size for the segregation of production and non production areas. There are further requirements for the segregation of pharmaceuticals and or components which have been tested and approved from those which have not. Sanitation and cleaning requirements are substantially equivalent.

## EQUIPMENT CLEANING AND MAINTENANCE

Once again, both the U.S. and Canada have substantially equivalent requirements with regard to equipment cleaning and maintenance. The Canadian provisions are found at C.02.005. The U.S. provisions are found at 21 CFR Sec. 211.67. Both regulations require that equipment be properly
cleaned, sanitized and maintained to prevent contamination by the addition of extraneous material to the product and to permit the proper functioning of the equipment. Records are to be created and maintained with regard to cleaning and maintenance. These regulations apply not only to equipment used in the manufacture and packaging of pharmaceuticals, but also to equipment used in storage.

## DRUG PRODUCT PACKAGING / CONTAINERS

The U.S. and Canada have substantially equivalent requirements regarding drug product containers. The Canadian provisions are found at C.02.016 and C.02.017. The U.S. provisions are found at 21 CFR Sec. 211.80, 21 CFR Sec. 211.82 and 21 CFR Sec. 211.89. There are some differences. The Canadian regulations deal only with packaging material prior to its use in the packaging of a drug, whereas the U.S. regulations deal with both components and drug product containers. Both countries require that packaging materials be tested or examined to ensure that materials of acceptable quality are used in the packaging of drugs. Identification, proper storage to prevent contamination, handling, sampling, testing, and approval or rejection of drug product containers and closures are also required.

## MANUFACTURING CONTROL

The U.S. and Canada both have requirements regarding manufacturing control which are substantially equivalent. The Canadian provision is found at C.02.011. The U.S. provisions are found at 21 CFR Sec. 211.100, 21 CFR Sec. 211.122, 21 CFR Sec. 211.125, 21 CFR Sec. 211.130 and 21 CFR Sec. 211.137. Although the Canadian regulation itself is very short, the interpretation of the regulation is longer than the four U.S. regulations combined. Both sets of regulatory provisions require written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. There are requirements for the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials. There are requirements to assure that the correct labels, labeling, and packaging materials are used for drug products. There are requirements for proper storage.

This primary level of regulation is probably the most critical for all following storage and warehousing of pharmaceuticals. It is at this level for manufacturers that all components are to be tested, the pharmaceutical properly formulated, packaged and labeled. Labeling requirements include information on temperature, humidity, light and other proper storage procedures. Labeling requirements will also include the expiration date. All subsequent storage and or warehousing of the pharmaceutical will be premised upon its initial labeling and any other accompanying written procedures.

## DISTRIBUTION

Substantially equivalent requirements exist in both Canada and the U.S. for distribution of the pharmaceutical product. The Canadian provision is found at C.02.012. The U.S. provision is found at 21 CFR Sec. 211.150. The primary purpose of both regulatory provisions appear to be the maintenance of procedures and records to facilitate the recall of the pharmaceutical if necessary. The U.S. provision also requires that the oldest approved stock be distributed first.

## RECORDS

The Canadian record provisions are found primarily at C.02.020, C.02.021, C.02.022, C.02.023 and C.02.024. The U.S. provisions are found at primarily 21 CFR Sec. 211.188 and 21 CFR Sec. 211.196. The regulatory provisions for both countries require that records be kept on virtually every aspect of pharmaceutical production, raw material testing, finished product testing, container testing, label verification, sanitation and storage. These procedures require that records be kept at virtually every level in the life of the pharmaceutical from initial raw material

and finished product testing to the ultimate destination of the pharmaceutical, whether it be rejected at one of the levels of production or distribution, whether it be recalled or whether in ultimately reach a consumer.

## MISCELLANEOUS

The U.S. has two regulatory provisions which do not appear to fit precisely with a specific Canadian counterpart. However, the requirements of these two sections are addressed in the Canadian regulations under the Quality Control Unit provisions of C02.013, C.02.014 and C.02.015. The U.S. regulations in question are 21 CFR Sec. 211.142 [Warehousing procedures] and 21 CFR Sec. 211.204 [Returned drug products]. 21 CFR Sec. 211.142 [Warehousing procedures] requires written procedures for drug products which include quarantining of drug products before release by the quality control unit and storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected. 21 CFR Sec. 211.204 [Returned drug products] requires that returned products be held until it has been determined that the conditions under which it has been previously held, stored, or shipped, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product. A returned drug product may be reprocessed if the subsequent drug product meets appropriate standards, specifications, and characteristics.

## CONCLUSION

As can be seen from the analysis of the selected U.S. and Canadian pharmaceutical regulatory provisions, the two countries have comparable requirements at virtually every level for the warehousing and storage of pharmaceuticals. Each country requires quality control units to test and inspect both the product and its packaging. Each country requires segregation of untested, tested and approved or rejected pharmaceuticals. Each country requires that raw materials be tested before production and the finished product be tested after production and in subsequent distribution. Labeling requirements are substantially similar and labeling contains directions for storing the pharmaceutical under appropriate conditions of temperature, humidity, and light. Each country has building design and construction features which consider ventilation, air filtration, heating, cooling, sanitation and appropriate size for the segregation of production and non production areas and pharmaceuticals and or components which have been tested and approved or rejected. Each country has equivalent sanitation requirements for production and storage and each country has extensive record keeping requirement

| CANADA | U.S. |
|---|---|
| C02.013 Quality Control Department<br>C.02.014<br>C.02.015 | 21 CFR 211.22 Responsibilities of quality control unit |
| C.02.006. | Personnel Sec. 211.25 Personnel qualifications |
| C.02.004 Premises | Sec. 211.42 Design and construction features<br>Sec. 211.46 Ventilation, air filtration, air heating and cooling.<br>Sec. 211.56 Sanitation. |
| C.02.005 Equipment | Sec. 211.67 Equipment cleaning and maintenance |
| C.02.016 Packaging Material Testing.<br>C.02.017 | Sec. 211.80 General requirements<br>Sec. 211.82 Receipt and storage of untested, components, drug product containers, and closures.<br>Sec. 211.89 Rejected components, drug product containers, and closures |
| C.02.011 Manufacturing Control | Sec. 211.100 Written procedures; deviations<br>Sec. 211.122 Materials examination and usage criteria<br>Sec. 211.125 Labeling issuance.<br>Sec. 211.130 Packaging and labeling operations.<br>Sec. 211.137 Expiration dating. |
| **CANADA** | **U.S.** |
| C.02.012 | Sec. 211.150 Distribution procedures. |
| C.02.020 Records<br>C.02.021<br>C.02.022<br>C.02.023<br>C.02.024 | Sec. 211.188 Batch production and control records.<br>Sec. 211.196 Distribution records |
| | Sec. 211.142 Warehousing procedures.<br>Sec. 211.204 Returned drug products. |

**Exhibit A**

Excerpted from Canadian Good Manufacturing Practices Guidelines, 2002 Edition, Version 2
(http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gmp_guidelines_2002_entire_e.html)

[Comparable to 21 CFR 211.22]
Quality Control Department
Regulation
C.02.013
1. Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.
2. The quality control department referred to in subsection (1) shall be a distinct organizational unit that functions and reports to management independently of any other functional units including the manufacturing, processing, packaging or sales unit.
Rationale
Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures. This Regulation ensures that the necessary and relevant tests are actually carried out and that raw materials and packaging materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be incorporated into all activities and decisions concerning the quality of the product.
Although manufacturing and quality control personnel share the common goal of assuring that high-quality drugs are fabricated, their interests may sometimes conflict in the short run as decisions are made that will affect a company's output. For this reason, an objective and accountable quality control process can be achieved most effectively by establishing an independent quality control department. The independence of quality control from manufacturing is considered fundamental. The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under Regulation C.02.006.
Interpretation
1. A person responsible for making decisions concerning quality control requirements of the fabricator, packager/labeller, distributor, and importer, is on site or fully accessible to the quality control department and has adequate knowledge of on-site operations to fulfill the responsibilities of the position.
2. The quality control department has access to adequate facilities, trained personnel, and equipment in order to fulfill its duties and responsibilities.
3. Approved written procedures are available for sampling, inspecting, and testing raw materials, packaging materials, in-process drugs, bulk drugs, and finished products.
4. Quality control personnel have access to production areas for sampling and investigations as appropriate.

Regulation
C.02.014
1. No lot or batch of drug shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality control department.
2. A drug that is returned to the fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer thereof shall not be made available for further sale unless the sale of that drug is approved by the person in charge of the quality control department.
3. No lot or batch of raw material or of packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug, unless that material is approved for that use by the person in charge of the quality control department.
4. No lot or batch of a drug shall be reprocessed without the approval of the person in charge of the quality control department.
Rationale
The responsibility for the approval of all raw materials, packaging materials and finished products is vested in the quality control department. It is very important that adequate controls be exercised by this department in order to guarantee the quality of the end product.

To maintain this level of quality, it is also important to examine all returned drugs and to give special attention to reprocessed drugs.

Interpretation

1. All decisions made by the quality control department pursuant to Regulation C.02.014 are signed and dated by the person in charge of the quality control department or by a designated alternate meeting the requirements described under Section C.02.006, Interpretation 1.4 or Interpretation 3.1 as applicable to the activity.

2. The assessment for the release of finished products embraces all relevant factors, including the production conditions, the results of in-process testing, the fabrication and packaging documentation, compliance with the finished product specifications, an examination of the finished package, and if applicable, a review of the transportation conditions.

2.1 Deviations and borderline conformances are evaluated in accordance with a written procedure. The decision and rationale are documented. Where appropriate, batch deviations are subject to trend analysis.

3. The quality control department ensures that raw materials and packaging materials are quarantined, sampled, tested, and released prior to their use in the fabrication or packaging/labelling of a drug.

4. Finished products returned from the market are destroyed unless it has been ascertained that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed in accordance with a written procedure. The reason for the return, the nature of the product, the **storage** conditions, the product's condition and history, and the time elapsed since it was originally sold are to be taken into consideration in this assessment. Records of any action taken are maintained.

5. Rejected materials and products are identified as such and quarantined. They are either returned to the vendors, reprocessed, or destroyed. Actions taken are recorded.

6. The reworking of any lot or batch of drug is given prior approval by the quality control department. Approval of a reworked lot or batch of a drug by the quality control department is based on documented scientific data, which may include validation. The reworking of products that fail to meet their specifications is undertaken only in exceptional cases. Reworking is permitted only when the following conditions are met:

- The quality of the finished product is not affected;
- The reworked lot meets specifications;
- If it is done in accordance with a defined procedure approved by the quality control department;
- All risks have been evaluated;
- Complete records of the reworking are kept;
- A new batch number is assigned; and
- The reworked lot is included in the ongoing stability program.

7. The reprocessing of any lot or batch of drug is given prior approval by the quality control department. Approval of a reprocessed lot or batch of a drug by the quality control department is based on documented scientific data, which may include validation. The reprocessing of products that fail to meet their specifications is undertaken only in exceptional cases. Reprocessing is permitted only when the following conditions are met:

- The quality of the finished product is not affected;
- The reprocessed lot meets specifications;
- The reprocessing is done in accordance with a defined procedure approved by the quality control department;
- All risks have been evaluated;
- Complete records of the reprocessing are kept;
- A new batch number is assigned; and
- Validation demonstrates that the quality of the finished product is not affected.

8. Recovery is not considered to be either a reprocessing or a reworking operation. Guidance regarding recovery is found under Regulation C.02.011, Interpretation 28.1.

9. The need for additional testing of any finished product that has been reprocessed, or reworked, or into which a recovered product has been incorporated, is evaluated and acted on by the quality control department. A record is maintained.

Regulation

C.02.015

1. All fabrication, packaging/labelling, testing, **storage**, and transportation methods and procedures that may affect the quality of a drug shall be examined and approved by the person in charge of the quality control department before their implementation.

2. The person in charge of the quality control department shall cause to be investigated every complaint on quality that is received and cause corrective action to be taken where necessary.
3. The person in charge of the quality control department shall cause all tests or examinations required pursuant to this Division to be performed by a competent laboratory.
Rationale
Pharmaceutical processes and products must be designed and developed taking GMP requirements into account. Production procedures and other control operations are independently examined by the quality control department. Proper **storage**, transportation, and distribution of materials and products minimize any risk to their quality. Complaints may indicate problems related to quality. By tracing their causes, one can determine which corrective measures should be taken to prevent recurrence. Having tests carried out by a competent laboratory provides assurance that test results are genuine and accurate.
Written contracts for consultants and contract laboratories describe the education, training, and experience of their personnel and the type of services provided and are available for examination and inspection. Records of the activities contracted are maintained.
Interpretation
The quality control department is responsible for the following:
1. All decisions made pursuant to Regulation C.02.015. These decisions are signed and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4 or Interpretation 3.1 as applicable to the activity.
2. Ensuring that guidelines and procedures are in place and implemented for **storage** and transportation conditions, such as: temperature, humidity, lighting controls, stock rotation, sanitation, and any other precautions necessary to maintain the quality and safe distribution of the drug.
3. The sampling of raw materials, packaging materials, in-process drugs, bulk drugs, and finished products is carried out in accordance with detailed written procedures. Samples are representative of the batches of material from which they are taken.
4. All complaints and other information concerning potentially defective products are reviewed according to written procedures. The complaint is recorded with all the original details and thoroughly investigated. Appropriate follow-up action is taken after investigation and evaluation of the complaint. All decisions and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records. Complaint records are regularly reviewed for any indication of specific or recurring problems that require attention. The same procedures are applied to recalls.
5. Establishing a change control system to provide the mechanisms for ongoing process optimization and for assuring a continuing state of control. All changes are properly documented, evaluated, and approved by the quality control department and are identified with the appropriate effective date. Any significant change may necessitate re-validation.
6. The tests are performed by a laboratory that meets all relevant GMP requirements.
6.1 Laboratory facilities are designed, equipped, and maintained to conduct the required testing.
6.2 The individual in charge of the laboratory either (a) is an experienced university graduate who holds a degree in a science related to the work being carried out and has practical experience in his or her responsibility area or (b) reports to a person who has these qualifications (C.02.006, Interpretation 1).
6.3 Laboratory personnel are sufficient in number and are qualified to carry out the work they undertake.
6.4 Laboratory control equipment and instruments are suited to the testing procedures undertaken. Equipment is serviced and calibrated at suitable intervals according to an approved procedure, and records are maintained.
6.5 Sensitive apparatus are protected against conditions (e.g., humidity, temperature, vibration, etc.) that may affect their functioning.
6.6 All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are labelled. Both positive and negative controls are applied to verify the suitability of culture media. The size of the inoculums used in positive controls relates to the required sensitivity. Records are maintained.

6.7 Reference standards are available in the form of the current reference standards listed in Schedule B to the Food and Drugs Act. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals. All reference standards are **stored** and used in a manner that will not adversely affect their quality. Records relating to their testing, **storage**, and use are maintained.

[Comparable to 21 CFR 211.25]
Personnel
Regulation
C.02.006
Every lot or batch of a drug shall be fabricated, packaged/labelled, tested, and **stored** under the supervision of personnel who, having regard to the duties and responsibilities involved have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser.
Rationale
People are the most important element in any pharmaceutical operation, without the proper personnel with the right attitude and the right training, it is almost impossible to fabricate, package/label, test, or store good quality drugs.
It is essential that qualified personnel be employed to supervise the fabrication of drugs. The operations involved in the fabrication of drugs are highly technical in nature and require constant vigilance, attention to details and a high degree of competence on the part of employees. Inadequate training of personnel or the absence of an appreciation of the importance of production control, often accounts for the failure of a product to meet the required standards.
Interpretation
1. For fabricators, packagers/labellers and testers, individuals in charge of the manufacturing department and the quality control department;
1.1 hold a university degree or equivalent in a science related to the work being carried out;
1.2 have practical experience in their responsibility area;
1.3 directly control and personally supervise on site, activities under their control; and
1.4 can delegate their duties and responsibility to a person in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years' relevant practical experience, while remaining accountable for those duties and responsibility.
2. Individuals responsible for packaging operations, including control over printed packaging materials and withdrawal of bulk drugs;
2.1 are qualified by training and experience; and
2.2 are directly responsible to the person in charge of the manufacturing department or a person having the same qualifications.
3. For distributors, importers, and wholesalers, individuals in charge of the quality control department;
3.1 are qualified by pertinent academic training and experience; and
3.2 can delegate their duties and responsibilities to a person who meets the requirements defined under Regulation C.02.006 Interpretation 3.1.
4. An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities are available on site.
4.1 The responsibilities placed on any one individual are not so extensive as to present any risk to quality.
4.2 All responsible personnel have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.
4.3 When key personnel are absent, qualified personnel are appointed to carry out their duties and functions.
5. All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities.

5.1 Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the fabrication of a drug, including technical, maintenance, and cleaning personnel.
5.2 The effectiveness of continuing training is periodically assessed.
5.3 Training is provided prior to implementation of new or revised SOPs.
5.4 Records of training are maintained.

5.5 Personnel working in areas where highly active, toxic, infectious, or sensitizing materials are handled are given specific training.
5.6 The performance of all personnel is periodically reviewed.
6. Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained.

[Comparable to 21 CFR 211.42, 211.46, 211.56]
C.02.004 Premises

The premises in which a lot or batch of a drug is fabricated or packaged/labelled shall be designed, constructed and maintained in a manner that; a. permits the operations therein to be performed under clean, sanitary and orderly conditions; b. permits the effective cleaning of all surfaces therein; and c. prevents the contamination of the drug and the addition of extraneous material to the drug.

Rationale

The pharmaceutical establishment should be designed and constructed in a manner such that it permits cleanliness and orderliness while preventing contamination. Regular maintenance is required to prevent deterioration of the premises. The ultimate objective of all endeavours is product quality.

Interpretation

1. Buildings are located in an environment that, when considered together with measures being taken to protect the manufacturing processes, presents a minimum risk of causing any contamination of materials or drugs.
2. The premises are designed, constructed, and maintained such that they prevent the entry of insects and other animals into the building and also prevent the migration of extraneous material from the outside into the building and from one area to another.

2.1 Doors, windows, walls, ceilings, and floors are such that no holes or cracks are evident (other than those intended by design).
2.2 Doors giving direct access to the exterior from manufacturing and packaging areas are used for emergency purposes only. These doors are adequately sealed. Receiving and shipping area(s) do not allow direct access to production areas.
2.3 Production areas are segregated from all non-production areas. Individual manufacturing, packaging, and testing areas are clearly defined and if necessary segregated. Areas where biological, microbiological or radioisotope testing is carried out require special design and containment considerations.
2.4 Laboratory animals' quarters are segregated.
2.5 Engineering, boiler rooms, generators, etc. are isolated from production areas.
3. In all areas where raw materials, in-process drugs, or drugs are exposed, the following considerations apply to the extent necessary to prevent contamination. In laboratories these considerations apply only to the extent necessary to ensure the validity of test results.
3.1 Floors, walls, and ceilings permit cleaning. Brick, cement blocks, and other porous materials are sealed. Surface materials that shed particles are avoided.
3.2 Floors, walls, ceilings, and other surfaces are hard, smooth and free of sharp corners where extraneous material can collect.
3.3 Joints between walls, ceilings and floors are sealed.
3.4 Pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned.
3.5 Floor drains are screened and trapped.

3.6 Air quality is maintained through dust control, monitoring of pressure differentials between production areas and periodic verification and replacement of air filters. The air handling system is well defined, taking into consideration airflow volume, direction, and velocity. Air handling systems are subject to periodic verification to ensure compliance with their design specifications. Records are kept.
4. Temperature and humidity are controlled, where required, in order to safeguard sensitive materials (e.g. raw materials, drugs, samples, reference standards, etc.).
5. Rest, change, wash-up, and toilet facilities are well separated from production areas and are sufficiently spacious, well ventilated, and of a type that permits good sanitary practices.
6. Premises layout is designed to avoid mix-ups and generally optimize the flow of personnel and materials.
6.1 There is sufficient space for receiving and all production activities.
6.2 Working spaces allow the orderly and logical placement of equipment (including parts and tools) and materials.
6.3 Where physical quarantine areas are used, they are well marked, with access restricted to designated personnel. Where electronic quarantine is used, electronic access is restricted to designated personnel.
6.4 A separate sampling area is provided for raw materials. If sampling is performed in the **storage** area, it is conducted in such a way as to prevent contamination or cross-contamination.
6.5 Working areas are well lit.
7. Utilities and support systems (e.g., HVAC, dust collection, and supplies of purified water, steam, compressed air, nitrogen, etc.) are qualified and are subject to periodic verification.
8. Outlets for liquids and gases used in the production of drugs are clearly identified as to their content.9. Premises are maintained in a good state of repair. Repair and maintenance operations do not affect drug quality.
10 Where necessary, separate rooms are provided and maintained to protect analytical instruments and associated control systems from vibration, electrical interference, and contact with excessive moisture or other external factors.
11. Prevention of cross-contamination during manufacturing is the responsibility of the fabricator and packager. They must demonstrate that the premises are designed in such a manner that the risk of cross-contamination between products is minimized.
11.1 In order to minimize the risk of a serious health hazard due to cross-contamination, additional controls, including the need for self-containment should be considered for particular drugs, such as the following:
- highly sensitizing drugs (e. g., penicillins)
- biologicals (e. g., live vaccines)
- certain hormones (e. g., estrogen)
- certain cytotoxic drugs
- other highly active drugs

Factors to consider are the manufacturing processes, the use of closed systems, dedication of product contact equipment parts, HVAC controls, and engineering controls (such as fail-safe systems), coupled with validation and ongoing monitoring using highly sensitive analytical methods.
11.2 Campaign production can be accepted where, on a product by product basis, proper justification is provided, validation is conducted and rigorous validated controls and monitoring are in place and demonstrate the minimization of any risk of cross-contamination.
11.3 No production activities of highly toxic non-pharmaceutical materials, such as pesticides and herbicides, are conducted in premises used for the production of drugs.
11.4 Once the products are enclosed in their immediate final containers, co- mingle **storage** in **warehouses** is allowed.
Self-contained facility means premises that provide complete and total separation of all aspects of the operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air handling systems. Self-contained facilities does not necessarily imply two distinct and separate buildings.

[comparable to 21 CFR 211.67]
Equipment

Regulation
C.02.005

The equipment with which a lot or batch of a drug is fabricated, packaged/labelled, or tested shall be designed, constructed, maintained, operated, and arranged in a manner that:
a. permits the effective cleaning of its surfaces;b. prevents the contamination of the drug and the addition of extraneous material to the drug; and
c. permits it to function in accordance with its intended use.
Rationale
The purpose of these requirements is to prevent the contamination of drugs by other drugs, by dust, and by foreign materials such as rust, lubricant and particles coming from the equipment. Contamination problems may arise from poor maintenance, the misuse of equipment, exceeding the capacity of the equipment and the use of worn-out equipment. Equipment arranged in an orderly manner permits cleaning of adjacent areas and does not interfere with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials. The fabrication of drugs of consistent quality requires that equipment perform in accordance with its intended use.
Interpretation
1. The design, construction and location of equipment permit cleaning, sanitizing, and inspection of the equipment.
1.1 Equipment parts that come in contact with raw materials, in-process drugs or drugs are accessible to cleaning or are removable.
1.2 Tanks used in processing liquids and ointments are equipped with fittings that can be dismantled and cleaned. Validated Clean-In-Place (CIP) equipment can be dismantled for periodic verification.
1.3 Filter assemblies are designed for easy dismantling.
1.4 Equipment is located at a sufficient distance from other equipment and walls to permit cleaning of the equipment and adjacent area.
1.5 The base of immovable equipment is adequately sealed along points of contact with the floor.
1.6 Equipment is kept clean, dry and protected from contamination when **stored**.
2. Equipment does not add extraneous material to the drug.
2.1 Surfaces that come in contact with raw materials, in-process drugs or drugs are smooth and are made of material that is non-toxic, corrosion resistant, non-reactive to the drug being fabricated or packaged and capable of withstanding repeated cleaning or sanitizing.
2.2 The design is such that the possibility of a lubricant or other maintenance material contaminating the drug is minimized.
2.3 Equipment made of material that is prone to shed particles or to harbour microorganisms does not come in contact with or contaminate raw materials, in-process drugs or drugs.
2.4 Chain drives and transmission gears are enclosed or properly covered.
2.5 Tanks, hoppers and other similar fabricating equipment are equipped with covers.
3. Equipment is operated in a manner that prevents contamination.
3.1 Ovens, autoclaves and similar equipment contain only one raw material, in-process drug or drug at a time, unless precautions are taken to prevent contamination and mix-ups.
3.2 Equipment is not operated where contaminants may fall into the material.
3.3 Equipment is placed in such a way to optimize the flow of material and to minimize the circulation of personnel.
3.4 Equipment is located so that production operations undertaken in a common area are compatible and so that prevent cross contamination between such operations is prevented.
3.5 Fixed pipework is clearly labelled to indicate the contents and, where applicable, the direction of flow.
3.6 Dedicated production equipment is provided where appropriate.
3.7 Water purification, **storage**, and distribution equipment is operated in such a manner so as to ensure a reliable source of water of the appropriate chemical and microbial purity.
4. Equipment is maintained in a good state of repair when in use.
4.1 Where a potential for the contamination of the drug being fabricated or packaged exists, surfaces are free from cracks, peeling paint and other defects.
4.2 Gaskets are functional.
4.3 The use of temporary devices such as tape is avoided.

4.4 Equipment parts that come in contact with drugs are maintained in such a manner that drugs are fabricated or packaged within specifications.
5. Production equipment is designed, located, and maintained to serve its intended purpose.

5.1 Scales and other measuring equipment of an appropriate range and precision are available for production and control operations. Such equipment is calibrated on a scheduled basis, and corresponding records are kept.
5.2 Defective and unused equipment is removed from production and quality control areas or is at least clearly labelled as such.
5.3 Equipment intended to be used during the critical steps of fabrication, packaging/labelling, and testing is subject to installation and operational qualification. Equipment qualification is documented.
5.4 Automatic, mechanical, electronic, or other types of equipment including computerized systems that are used in the fabrication, packaging/labelling, and storing of a drug is routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of these calibration checks and inspections are maintained.
5.5 Equipment usage logs are maintained.

[Comparable to 21 CFR 211.80, 211.82, 211.89]

Packaging Material Testing
Regulation
C.02.016
1. Each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material.
2. No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.
3. The specifications referred to in subsections (1) and (2) shall
a. be in writing;
b. be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the Act; and
c. be approved by the person in charge of the quality control department.
Rationale
Where a drug product is presented in an inadequate package, the entire effort put into the initial research, product development and manufacturing control is wasted. Drug quality is directly dependent on packaging quality. In many cases (e.g., metered-dose aerosols), packaging quality is critical to the overall performance and effectiveness of the drug product. Faults in the packaging and labelling of a drug product continue to be a major cause of drug recalls. Packaging materials are required to be tested or examined prior to their use in a packaging operation to ensure that materials of acceptable quality are used in the packaging of drugs.
Interpretation
1. Each packaging material used in the packaging/labelling of a drug is covered by specifications (as defined under C.02.002) that are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4. The use of recycled or reprocessed primary packaging components is permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision is made for such a situation in the specifications.
2. Where applicable, specifications are of pharmacopoeial or equivalent status and are in compliance with the marketing authorization.
3. The adequacy of test or examination methods that are not of pharmacopoeial or equivalent status is established and documented.
4. Only packaging materials released by the quality control department are used in packaging/labelling.
5. Outdated or obsolete packaging material is adequately segregated until its disposition.

Regulation
C.02.017
1. The examination or testing referred to in section C.02.016 shall be performed on a sample taken

a. after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or

b. subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug, if
i.that person
A. has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials; and
B .undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director,
11. the packaging material has not been transported or **stored** under conditions that may affect its compliance with the specifications for that packaging material.
2. After a lot or batch of packaging material is received on the premises of the person who packages a drug,
a. the lot or batch of the packaging material shall be examined or tested for identity; and
b. the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.
Rationale
Regulation C.02.017 outlines options as to when the testing or examination prescribed by Regulation C.02.016 is carried out. As with raw materials, the purchase of packaging materials is an important operation that involves personnel who have a particular and thorough knowledge of the packaging materials and vendor.
Packaging materials originate only from vendors named in the relevant specifications. It is of benefit that all aspects of the production and control of packaging materials be discussed between the manufacturer and the vendor. Particular attention is paid to printed packaging materials; labels are examined or tested after receipt on the premises of the person who packages a drug.
Interpretation
1. The testing or examination of the packaging material is performed on a sample taken after their receipt on the premises of the person that packages the drug unless the vendor is certified. A packaging material vendor certification program, if employed, is documented in a standard operating procedure. The following approaches may be used for vendor certification:
1.1 A written contract outlines the specific responsibilities of each party involved. As a minimum, that contract specifies the following:
1.1.1 all the tests to be performed by the vendor, along with the content and format of the certificate of analysis, which exhibits actual numerical results, if applicable, and makes reference to product specifications.
1.1.2 that the vendor must inform the drug packager/labeller of any changes in the processing or specifications of the packaging material; and
1.1.3 that the vendor must inform the drug packager/labeller of any critical deviations during the manufacturing of a particular batch of a packaging material.
1.2 In lieu of a contract, an on-site audit of the vendor's facilities and controls by qualified personnel is acceptable. The audit ensures that all criteria described under Interpretation 1.1 are verified. These audits are performed at an appropriate frequency, and the results are documented.
2. The certification procedure also outlines how re-testing failures and any subsequent re-qualification is to be addressed.
3. A document is issued for each vendor verifying that the certification criteria have been met. The document is approved by the quality control department and is updated at an appropriate frequency.
4. When a certification program is implemented, complete confirmatory examination or testing of a minimum of one lot per year per vendor is required for non-printed packaging material.
5. Generally, due to the nature of its operations, a broker or wholesaler of packaging materials cannot be directly certified. However, when evidence is available that all original labels, certificate of analysis, general information, and package supplied by the original vendor of the packaging material has not been altered in any way during the distribution sequence, certification of the original source is still acceptable.
6. Provided that the material is properly identified, a lot or batch of packaging material selected for confirmatory testing may, with the approval of the quality control department, be used in packaging prior to completion of that testing.

7. Conditions of transportation and **storage** are such that they prevent alterations of the characteristics of the packaging material. In order to demonstrate that these conditions have been met, standard operating procedures and records are available and contain the following:

7.1 the type of packaging to be employed;
7.2 labelling requirements;
7.3 mode of transportation;
7.4 the type of seal used on the package; and
7.5 the verification required to ensure that the package has not been tampered with and that there are no damaged containers.
8. Positive identification on all packaging materials, along with examination of all labels and other printed packaging materials, is conducted following their receipt on the premises of the person who packages the drug.
9. If a delivery or shipment of packaging material is made up of different batches, each batch is considered as separate for the purposes of sampling, testing, and release.

[Comparable to 21 CFR 211.100, 211.122, 211.125, 211.130]

Manufacturing Control
Regulation
C.02.011
1. Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug shall have written procedures, prepared by qualified personnel, in respect of the drug to ensure that the drug meets the specifications for use of that drug.
2. Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.
Rationale
This Regulation requires that a number of measures be taken to maintain the integrity of a drug product from the moment the various raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to ensure that all manufacturing processes are clearly defined, systematically reviewed in light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their established specifications.
Interpretation
1. All handling of materials and products, such as receipt, quarantine, sampling, **storage**, tracking, labelling, dispensing, processing, packaging and distribution is done in accordance with approved written procedures or instructions and recorded.
2. All critical production processes are validated. Detailed information is provided in Health Canada's Validation Guidelines for pharmaceutical dosage forms.
3. Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is prepared, evaluated, approved, and maintained.
4. Changes to production processes, equipment, or materials that may affect product quality and/or process reproducibility are validated prior to implementation.
5. Any deviation from instructions or procedures is avoided. If deviations occur, qualified personnel write a report that describes the deviation, the investigation, the rationale for disposition, and any follow-up activities required. The report is approved by the quality control department.
6. Checks on yields and reconciliation of quantities are carried out at appropriate stages of the process to ensure that yields are within acceptable limits.
7. Deviations from the expected yield are recorded and investigated.
8. Access to production premises is restricted to designated personnel.
9. Provided that changeover procedures are validated and implemented, non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of pharmaceutical products.
10. Before any processing operation is started, steps are taken and documented to ensure that the work area and equipment are clean and free from any raw materials, products, product residues, labels, or documents not required for the current operation.

11.In-process control activities that are performed within the production areas do not pose any risk to the quality of the product.
12. Measuring devices are regularly checked for accuracy and precision, and records of such checks are maintained.
13. At all times during processing, all materials, bulk containers, major items of equipment and the rooms used are labelled or otherwise identified with an indication of the product or material being processed, its strength, and the batch number.
14. Rejected materials and products are clearly marked as such and are either **stored** separately in restricted areas or controlled by a system that ensures that they are either returned to their vendors or, where appropriate, reprocessed or destroyed. Actions taken are recorded.
15. Equipment is located so that production operations undertaken in a common area are compatible.
16. Upon receipt, bulk drugs, in-process (intermediate) drugs, raw materials, and packaging materials are accounted for and **held** in quarantine until released by the quality control department.
17.Procedures are in place to ensure the identity of the contents of each container. Containers from which samples have been drawn are identified.
18. For each consignment, all containers are checked for integrity of package and seal and to verify that the information on the order, the delivery note and the vendor's labels is in agreement.
19. Damage to containers, along with any other problem that might adversely affect the quality of a material, is recorded, reported to the quality control department, and investigated.
20. Upon receipt, containers are cleaned where necessary and labelled with the prescribed data.
21. Labels for bulk drugs, in-process drugs, raw materials, and packaging materials bear the following information:
21.1 the designated name of the material and a code reference where applicable;21.2 the specific batch number(s) given by the vendor and on receipt by the fabricator or packager/labeller;
21.3 the status of the contents (e.g., in quarantine, on test, released, rejected, to be returned or recalled) appears on the label when a manual system is used;
21.4 an expiry date or a date beyond which re-testing is necessary.Note: When fully computerized storage systems are used, backup systems are available in case of system failure to satisfy the requirements of Interpretation 21.
22. Raw materials are dispensed and verified by qualified personnel, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
Manufacturing Master Formula
23. Processing operations are covered by master formulae, that are prepared by, and are subject to independent checks by, persons who have the qualifications described under Regulation C.02.006 Interpretation 1.
24. Master formulae are written to provide not less than 100% of label claim and include the following:
24.1 the name of the product, with a reference code relating to its specifications;
24.2 a description of the dosage form, strength of the product, and batch size;
24.3 a list of all raw materials to be used, along with the amount of each, described using the designated name and a reference that is unique to that material (mention is made of any processing aids that may not be present in the final product);
24.4 a statement of the expected final yield, along with the acceptable limits, and of relevant intermediate yields, where applicable;
24.5 a statement of the principal equipment to be used;
24.6 the procedures, or reference to the procedures, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing, etc.;
24.7 detailed stepwise processing instructions (e.g., checks on materials, pretreatment, sequence for adding materials, mixing times or temperatures, etc.);
24.8 the instructions for any in-process controls, along with their limits;
24.9 where necessary, the requirements for **storage** of the products, including the container, the labelling and any special **storage** conditions; and
24.10 any special precautions to be observed.
Packaging Master Formula
25. In the case of a packaged product, the master formula also includes for each product, package size and type, the following:

25.1 the package size, expressed in terms of the number, weight, or volume of the product in the final container;
25.2 a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code or reference number relating to the specifications for each packaging material;
25.3 an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product are to be positioned;
25.4 special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;
25.5 a description of the packaging operations, including any significant subsidiary operations and the equipment to be used; and
25.6 details of in-process controls, with instructions for sampling and acceptance limits.
anufacturing Batch Document
26. Each batch processed is effectively governed by an individually numbered manufacturing order prepared by qualified personnel from the master formula by such means as to prevent errors in copying or calculation and verified by qualified personnel.27. As it becomes available during the process, the following information is included on or with the manufacturing order:
27.1 the name of the product;
27.2 the number of the batch being manufactured;
27.3 dates and times of commencement and completion of significant intermediate stages, such as blending, heating, etc., and of production;
27.4 the batch number and/or analytical control number, as well as the quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 98% calculated on "as is" basis and on which the master formula was based);
27.5 confirmation by qualified personnel of each ingredient added to a batch;
27.6 the identification of personnel performing each step of the process; and of the person who checked each of these steps;
27.7 the actual results of the in-process quality checks performed at appropriate stages of the process and the identification of the person carrying them out;
27.8 the actual yield of the batch at appropriate stages of processing and the actual final yields, together with explanations for any deviations from the expected yield;
27.9 detailed notes on special problems with written approval for any deviation from the master formula; and
27.10 after completion, the signature of the person responsible for the processing operations.
28. Batches are combined only with the approval of the quality control department and according to pre-established written procedures.
28.1 The introduction of part of a previous batch, conforming to the required quality, into the next batch of the same product at a defined stage of fabrication is approved beforehand. This recovery is carried out in accordance with a validated procedure and is recorded.
Packaging Batch Document
29. Packaging operations are performed according to comprehensive and detailed written operating procedures or specifications, which include the identification of equipment and packaging lines used to package the drug, the adequate separation and if necessary, the dedication of packaging lines that are packaging different drugs and disposal procedures for unused printed packaging materials. Packaging orders are individually numbered.
30. The method of preparing packaging orders is designed to avoid transcription errors.
31. Before any packaging operation begins, checks are made that the equipment and work station are clear of previous products, documents, and materials that are not required for the planned packaging operations and that equipment is clean and suitable for use. These checks are recorded.
32. All products and packaging materials to be used are checked on receipt by the packaging department for quantity, identity and conformity with the packaging instructions.
33. Precautions are taken to ensure that containers to be filled are free from contamination with extraneous material.
34. The name and batch number of the product being handled is displayed at each packaging station or line.

35. Packaging orders include the following information (recorded at the time each action is taken):
35.1 the date(s) and time(s) of the packaging operations;
35.2 the name of the product, the batch number, and the quantity of bulk product to be packaged, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
35.3 the identification of the personnel who are supervising packaging operations and the withdrawal of bulks;
35.4 the identification of the operators of the different significant steps;
35.5 the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
35.6 the general appearance of the packages;
35.7 whether the packages are complete;
35.8 whether the correct products and packaging materials are used;
35.9 whether any on-line printing is correct;
35.10 the correct functioning of line monitors;
35.11 handling precautions applied to a partly packaged product;
35.12 notes on any special problems, including details of any deviation from the packaging instructions with written approval by qualified personnel;
35.13 the quantity, lot number, and/or analytical control number of each packaging material and bulk drug issued for use; and
35.14 a reconciliation of the quantity of printed packaging material and bulk drug used, destroyed or returned to stock.
36. To prevent mix-ups, samples taken away from the packaging line are not returned.
37. Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting, are attached to packaging orders.
38. Filling and sealing are followed as quickly as possible by labelling. If labelling is delayed, procedures are applied to ensure that no mix-ups or mislabelling can occur.
39. Upon completion of the packaging operation, any unused batch-coded packaging materials are destroyed, and their destruction is recorded. A procedure is followed if non-coded printed materials are returned to stock.
40. Outdated or obsolete packaging materials are destroyed and their disposal is recorded.
41. Products that have been involved in non-standard occurrences during packaging are subject to inspection and investigation by qualified personnel. A detailed record is kept of this operation.42. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release. Validated electronic verification of all printed packaging materials on the packaging line may obviate the need for their full reconciliation.
43. Printed packaging materials are
43.1 **stored** in an area to which access is restricted to designated personnel who are supervised by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2;
43.2 withdrawn against a packaging order;43.3 issued and checked by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2; and
43.4 identified in such a way as to be distinguishable during the packaging operations.
44. To prevent mix-ups, roll-fed labels are preferred to cut labels. Gang printing is avoided.
45. Cut labels, cartons, and other loose printed materials are **stored** and transported in separate closed containers.
46. Special care is taken when cut labels are used, when overprinting is carried out off-line and in hand-packaging operations. On line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Checks are made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
47. The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging is checked and recorded.
48. Raw materials, packaging materials, intermediates, bulk drugs and finished products are (a) **stored** in locations that are separate and removed from immediate manufacturing areas, and (b) transported under conditions designated by the quality control department to preserve their quality and safety.

49. All intermediate and finished products are **held** in quarantine and are so identified in accordance with Interpretation 21, until released by the quality control department.
50. Every package of a drug is identified by a lot number.

[Comparable to 21 CFR 211.150]

Regulation
C.02.012
1. Every fabricator, packager/labeller or distributor referred to in section C.01A.003, importer, and wholesaler of a drug shall maintain
a. a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and
b. a program of self-inspection.
2. Every fabricator and packager/labeller and subject to subsections (3) and (4), every distributor referred to in section C.01A.003(b) and importer of a drug shall maintain a system designed to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.
3. The distributor referred to in paragraph C.01A.003(b) of a drug that is fabricated, packaged/labelled, and tested in Canada by a person who holds an establishment licence that authorizes those activities is not required to comply with the requirements of subsection (2) in respect of that drug.
4. If a drug is fabricated or packaged/labelled in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of the drug is not required to comply with the requirements of subsection (2) in respect of that activity for that drug if
a. the address of the building is set out in that person's establishment licence; and
b. that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.
Rationale
The purpose of a recall is to remove from the market, a drug that represents an undue health risk.
Drugs that have left the premises of a fabricator, packager/labeller, distributor, wholesaler and importer can be found in a variety of locations. Depending on the severity of the health risk, it may be necessary to recall a product to one level or another. Fabricators, packagers/labellers, distributors, wholesalers, and importers are expected to be able to recall to the consumer level if necessary. Additional guidance on recalls can be found in the Heath Canada document titled "Product Recall Procedures".
This Regulation also requires fabricators, packagers/labellers, distributors, wholesalers, and importers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate the compliance with GMP in all aspects of production and quality control. The self-inspection program is designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
Drugs offered for sale in Canada, regardless of whether they are domestically produced or are imported, must meet the requirements of the GMP Division of the Food and Drug Regulations. Contract production and analysis must be correctly defined, agreed on, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. Normally, a contract or other written agreement exists between the parties involved, and that document clearly establishes the duties of each party.
Interpretation
1. A written recall system is in place to ensure compliance with Section C.01.051 of the Food and Drug Regulations and requires the following:
1.1 Health Canada is to be notified of the recall.
1.2 Action that is taken to recall a product suspected or known to be in violation is prompt and in accordance with a pre-determined plan; the procedures to be followed are in writing and are known to all concerned.
1.3 The person(s) responsible for initiating and co-ordinating all recall activities are identified.
1.4 The recall procedure is capable of being put into operation at any time, during and outside normal working hours.

1.5 The recall procedure outlines the means of notifying and implementing a recall and of deciding its extent.

1.6 Distribution records enable tracing of each drug product, and account is taken of any products that are in transit, any samples that have been removed by the quality control department, and any professional samples that have been distributed.
1.7 Recalled products are identified and are **stored** separately in a secure area until their disposition is determined.
1.8 The progress and efficacy of the recall is assessed and recorded at intervals, and a final report is issued (including a final reconciliation).
1.9 All Canadian and foreign establishments involved in the fabrication, distribution, or importation of the recalled product are notified.
2. A self-inspection program appropriate to the type of operations of the company, in respect to drugs, ensures compliance with Division 2, Part C of the Food and Drug Regulations.
2.1 A comprehensive written procedure that describes the functions of the self-inspection program is available.
2.2 The program of a fabricator engaged in processing a drug from raw material through to the drug in dosage form addresses itself to all aspects of the operation. For packagers/labellers, distributors, importers, and wholesalers engaged only in packaging and/or distributing drugs fabricated by another fabricator, the written program covers only those aspects of the operations over which they exercise control on their premises.
2.3 The self-inspection team includes personnel who are suitably trained and qualified in GMP.
2.4 Periodic self-inspections are carried out.
2.5 Reports on the findings of the inspections and on corrective actions are reviewed by appropriate senior company management. Corrective actions are implemented in a timely manner.
3. To ensure compliance of contract fabricators and packagers/labellers:
3.1 All arrangements for contract fabrication or packaging/labelling and testing are in accordance with the marketing authorization for the drug product concerned.
3.2 There is a written contract or other agreement covering the fabrication or packaging/labelling and/or analysis arranged among the parties involved. The contract or agreement specifies their respective responsibilities relating to the fabrication or packaging/labelling and control of the product.
3.2.1 Technical aspects of the contract or agreement are drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, analysis, and GMP.
3.2.2 The contract or agreement permits the distributor or importer to audit the facilities of the contractor.
3.2.3 The contract or agreement clearly describes who is responsible for:
- purchasing, sampling, testing, and releasing materials
- undertaking production, quality, and in-process controls
- process validation
- test method validation
3.2.4 The contract specifies the way in which the quality control department of the distributor or importer releasing the lot for batch for sale, ensures that each lot or batch has been fabricated and packaged/labelled in compliance with the requirements of the marketing authorization.
3.2.5 The contract describes the handling of raw materials, packaging materials, in-process drug, bulk drug and finished products if they are rejected.
3.3 The contractor's complaint/recall procedures specify that any records relevant to assessing the quality of a drug product in the event of complaints or a suspected defect are accessible to the distributor or importer.
3.4 The fabricator, packager/labeller, distributor, or importer provides the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The fabricator, packager/labeller, distributor, or importer ensures that the contractor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.
3.5 The fabricator, packager/labeller, distributor, or importer is responsible for assessing the contractor's continuing competence to carry out the work or tests required in accordance with the principles of GMP described in these guidelines.
3.5.1 Distributors of drugs fabricated, packaged/labelled and tested at Canadian sites are required only to have a copy of the relevant valid Canadian establishment licence **held** by the Canadian fabricator or packager/labeller or tester.

3.5.2 Importers of drugs fabricated, packaged/labelled, or tested at a foreign site must meet the requirements described in the policy titled Conditions for Acceptance for Foreign Inspection Reports.

[Comparable to 21 CFR 211.137, 211.188, 211.196]
Records
Regulation
C.02.020
1. Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain on their premises in Canada for each drug sold
a. master production documents for the drug;
b. evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and **stored** in accordance with the procedures described in the master production documents;
c. evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and **stored** are in compliance with the requirements of this Division;
d. evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug; and
e. adequate evidence of the testing referred to in section C.02.018.
2. Every distributor referred to in paragraph C.01A.003(b) and importer shall make available on request the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of a drug sold.
3. Every fabricator shall maintain on his premises
a. the written specifications for the raw material; and
b. adequate evidence of the raw materials testing referred to in section C.02.009.
4. Every person who packages a drug shall maintain on his premises
a. the written specifications for the packaging materials; and
b. adequate evidence of the packaging material examination or testing referred to in section C.02.016.
5. Every fabricator shall maintain on their premises in Canada:
a. detailed plans and specifications of each building in Canada at which they fabricate, package/label or test; and
b. a description of the design and construction of those buildings.
6. Every fabricator, packager/labeller and tester shall maintain on their premises in Canada details of the personnel employed to supervise the fabrication, packaging/labelling and testing, including each person's title, responsibilities, qualifications, experience and training.

C.02.021
1. Subject to subsection (2), all records and evidence on the fabrication, packaging/labelling, testing and **storage** of a drug that are required to be maintained under this Division shall be retained for a period of at least one year after the expiration date on the label of the drug, unless otherwise specified in the person's establishment licence.
2. All records and evidence on the testing of raw materials and packaging/labelling materials that are required to be maintained under this Division shall be retained for a period of at least five years after the materials were last used in the fabrication or packaging/labelling of a drug unless otherwise specified in the person's establishment licence.

C.02.022
Every distributor referred to in section C.01A.003, wholesaler and importer of a drug shall retain records of the sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market for a period of at least one year after the expiration date of the lot or batch unless otherwise specified in their establishment licence.

C.02.023
1. On receipt of a complaint respecting the quality of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the complaint and of its investigation and retain the record for a period of at least one year after the expiration date of the lot or batch of the drug, unless otherwise specified in their establishment licence.

2. On receipt of any information respecting the quality or hazards of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the information and retain it for a period of at least one year after the expiration date of the lot or batch of the drug unless otherwise specified in their establishment licence.

C.02.024
1. Every fabricator, packager/labeller, distributor referred to in section C.01A.003 importer and wholesaler shall
a. maintain records of the results of the self-inspection program required by section C.02.012 and of any action taken in connection with that program; and
b. retain those records for a period of at least three years.
2. Every person who fabricates or packages/labels a drug shall
a. maintain records on the operation of the sanitation program required to be implemented under section C.02.007, and
b. retain those records for a period of at least three years.

Rationale
Good documentation is an essential part of the quality assurance system and should therefore be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of fabrication, packaging/labelling, and control; to ensure that the quality control department has all the information necessary to decide whether or not to release a batch of a drug for sale; and to provide an audit trail that will permit investigation of the history of any batch that is suspected to be defective.
Evidence that drugs have been fabricated and packaged/labelled under prescribed conditions can be maintained only after developing adequate record systems. The information and evidence should provide assurance that imported drugs are fabricated and packaged/labelled in a like manner to those produced in Canada.
Interpretation
For all sections of Good Manufacturing Practices guidelines, standard operating procedures (SOPs) are retained for reference and inspection. These SOPs are regularly reviewed and kept up to date by qualified personnel. The reasons for any revisions are documented. A system is in place to ensure that only current SOPs are in use. Records of SOPs for all computer and automated systems are retained where appropriate.
All relevant GMP documents (such as associated records of actions taken or conclusions reached) and SOPs are approved, signed, and dated by the quality control department. Documents are not altered without the approval of the quality control department. Any alteration made to a document is signed and dated; the alteration permits the reading of the original information. Where appropriate, the reason for the change is recorded.
Records may be maintained in electronic format provided that backup copies are also maintained. Electronic data must be readily retrievable in a printed format. During the retention period, such records must be secured and accessible within 48 hours to the fabricator, packager/labeller, distributor, or importer.
An electronic signature is an acceptable alternative to a handwritten signature. When used, such a system must be evaluated and tested for security, validity, and reliability, and records of those evaluations and tests must be maintained. The validation of electronic signature identification systems is documented.
Any documentation requested for evaluation by Health Canada is provided in one of the official languages.
1. The following documents are maintained by the fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug:1.1 Master production documents as defined in the Glossary of Terms.
1.1.1 When the fabricator is located in Canada, specific parts of a master production document considered to be a trade secret or confidential may be **held** by the fabricator rather than the distributor. When the fabricator is located outside Canada, specific parts of a master production document considered to be a trade secret or confidential may be **held** on behalf of the distributor or importer by an independent party in Canada. In either case, the distributor or importer must ensure that Health Canada has access to the data in a timely manner.1.1.2 Regardless of whether the fabricator is Canadian or foreign, the master production document retained by the distributor or importer describes in general terms whatever information has been deleted as a trade secret or confidential.

1.2 Evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and **stored** in accordance with the procedures described in the master production documents.
1.2.1 This evidence includes manufacturing orders, packaging orders, and test results for raw materials, packaging materials, and drugs in dosage form. However, when the drug is fabricated or packaged outside the premises of the distributor or importer, test results for raw materials and packaging materials need only be made available on request in a timely manner.
1.2.2 A certificate of manufacture is considered an acceptable alternative to complete batch documentation, provided that complete documentation is made available on request in a timely manner.
1.2.3. Where an importer of drugs from non-MRA countries employs a system involving a "certificate of manufacture", complete batch documentation is obtained at least once per year per drug.
1.2.4. A certificate of manufacture alone cannot be employed where reworking has taken place. Should there be changes to the production documents, the complete documentation is provided to the importer or distributor, and any changes that have been made are indicated.
1.3 Evidence that the conditions under which the drug was fabricated, packaged/labelled, tested, and **stored** are in compliance with requirements of this Division.
1.3.1 This evidence includes records generated under subsection C.02.012(2) and evidence of validation. For additional guidance, refer to the "Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers."
1.3.2 Records include the name, address, and qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides. Records of consultants' activities (contracts) are maintained.
1.4 Evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug.
1.4.1 The documentation to be maintained includes the written stability program, the data generated in accordance with that program, and the conclusions leading to the establishment of the period of time during which each drug in the package in which it is sold complies with the specifications for that drug. Also included are data generated as part of the continuing stability program.
1.5 For each lot of drug in dosage form, adequate evidence of compliance with finished product specifications.
2. The following documents are maintained by the fabricator, packager/labeller, distributor, wholesaler, and importer of a drug as they relate to all operations in Canada:
2.1 Distribution records of all sales of drugs, including those of professional samples.
2.1.1 Records of all sales are retained or are kept readily accessible in a manner that will permit a complete and rapid recall of any lot or batch of a drug. This requirement need not necessarily involve tracking by lot number.
2.1.2 Records to indicate that all customers who have received a recalled drug have been notified.
2.2 Records of the results of the self-inspection program, evaluation, and conclusions, and corrective measures implemented.
3. The following documents are maintained by every fabricator, packager/labeller, distributor, and importer of a drug:
3.1 Records of complaints relating to quality and of subsequent investigations of complaints, including corrective actions taken.
3.2 Records concerning information received respecting the quality or hazards of a drug.
4. The following documents are maintained by the fabricator:
4.1 the written specifications for the raw materials;
4.2 the results of the raw material testing;
4.3 the sources of the raw materials supplied;
4.4 records on the operation of the sanitation program required by Regulation C.02.007; and
4.5 detailed plans and specifications of each building where fabrication occurs, including a description of the design and construction.
5. The following documents are maintained by the person who packages or labels a drug:
5.1 the written specifications for the packaging materials;
5.2 the results of the packaging material examinations or testing;
5.3 the sources of the packaging materials supplied; and
5.4 records on the operation of the sanitation program required by Regulation C.02.007.
6. Every fabricator, packager/labeller, and tester maintains

6.1 Details of the personnel employed to supervise the fabrication, packaging/labelling, and testing, including organization charts; each person's title, job description, responsibilities, qualifications, experience, and training; and the name(s) of each person's designated alternate(s).
7.Records required under Regulations C.02.021(1), C.02.022, and C.02.023 are retained for a period of at least one year past the expiration date of the drug to which the records apply.
7.1 For medical gases, which do not require an expiration date, records required under Regulations C.02.021(1), C.02.022, and C.02.023 are retained for a period of at least five years from the date of fabrication of the drug.

## Exhibit B

Excerpted from Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1)

21 CFR 211.22 Responsibilities of quality control unit

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or **held** under contract by another company. (b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit. (c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product. (d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

Subpart B--Organization and Personnel Sec. 211.25 Personnel qualifications. (a) Each person engaged in the manufacture, processing, packing, or **holding** of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them. (b) Each person responsible for supervising the manufacture, processing, packing, or **holding** of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess. (c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or **holding** of each drug product.

Sec. 211.42 Design and construction features. (a) Any building or buildings used in the manufacture, processing, packing, or **holding** of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations. (b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination. (c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm`s operations as are necessary to prevent contamination or mixups during the course of the following procedures: (1) Receipt, identification, **storage**, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging; (2) **Holding** rejected components, drug product containers, closures, and labeling before disposition; (3) **Storage** of released components, drug product containers, closures, and labeling; (4) **Storage** of in-process materials; (5) Manufacturing and processing operations; (6) Packaging and labeling operations; (7) Quarantine **storage** before release of drug products; (8) **Storage** of drug products after release; (9) Control and laboratory operations; (10) Aseptic processing, which includes as appropriate: (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable; (ii) Temperature and humidity controls; (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar; (iv) A system for monitoring environmental conditions; (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions. (d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use. [43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

Subpart C--Buildings and Facilities Sec. 211.46 Ventilation, air filtration, air heating and cooling. (a) Adequate ventilation shall be provided. (b) Equipment for adequate control over air pressure, micro- organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or **holding** of a drug product. (c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants. (d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

Subpart C--Buildings and Facilities Sec. 211.56 Sanitation. (a) Any building used in the manufacture, processing, packing, or **holding** of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be **held** and disposed of in a timely and sanitary manner. (b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed. (c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135). (d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full- time employees during the ordinary course of operations.

Subpart D--Equipment Sec. 211.67 Equipment cleaning and maintenance. (a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing,

packing, or **holding** of a drug product. These procedures shall include, but are not necessarily limited to, the following: (1) Assignment of responsibility for cleaning and maintaining equipment; (2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules; (3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance; (4) Removal or obliteration of previous batch identification; (5) Protection of clean equipment from contamination prior to use; (6) Inspection of equipment for cleanliness immediately before use. (c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in Secs. 211.180 and 211.182.

Subpart E–Control of Components and Drug Product Containers and Closures Sec. 211.80 General requirements. (a) There shall be written procedures describing in sufficient detail the receipt, identification, **storage**, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed. (b) Components and drug product containers and closures shall at all times be handled and **stored** in a manner to prevent contamination. (c) Bagged or boxed components of drug product containers, or closures shall be **stored** off the floor and suitably spaced to permit cleaning and inspection. (d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Subpart E–Control of Components and Drug Product Containers and Closures Sec. 211.82 Receipt and **storage** of untested components, drug product containers, and closures. (a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination. (b) Components, drug product containers, and closures shall be **stored** under quarantine until they have been tested or examined, as appropriate, and released. **Storage** within the area shall conform to the requirements of Sec. 211.80.

Subpart E–Control of Components and Drug Product Containers and Closures Sec. 211.89 Rejected components, drug product containers, and closures. Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

Subpart F–Production and Process Controls Sec. 211.100 Written procedures; deviations. (a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

Subpart G–Packaging and Labeling Control Sec. 211.122 Materials examination and usage criteria. (a) There shall be written procedures describing in sufficient detail the receipt, identification, **storage**, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product. (b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable. (c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected. (d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be **stored** separately with suitable identification. Access to the **storage** area shall be limited to authorized personnel. (e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed. (f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color. (g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures: (1) Dedication of labeling and packaging lines to each different strength of each different drug product; (2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or (3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person. (h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

Subpart G–Packaging and Labeling Control Sec. 211.125 Labeling issuance. (a) Strict control shall be exercised over labeling issued for use in drug product labeling operations. (b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records. (c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with Sec. 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100- percent examination for correct labeling is performed in accordance with Sec. 211.122(g)(2). (d) All excess labeling bearing lot or control numbers shall be destroyed. (e) Returned labeling shall be maintained and **stored** in a manner to prevent mixups and provide proper identification. (f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

Subpart G–Packaging and Labeling Control Sec. 211.130 Packaging and labeling operations. There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features: (a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products. (b) Identification and handling of filled drug product containers that are set aside and **held** in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container. (c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch. (d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record. (e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

Subpart G–Packaging and Labeling Control Sec. 211.137 Expiration dating. (a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in Sec. 211.166. (b) Expiration dates shall be related to any **storage** conditions stated on the labeling, as determined by stability studies described in Sec. 211.166. (c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products. (d) Expiration dates shall appear on labeling in accordance with the requirements of Sec. 201.17 of this chapter. (e) Homeopathic drug products shall be exempt from the requirements of this section. (f) Allergenic extracts that are labeled ``No U.S. Standard of Potency`` are exempt from the requirements of this section. (g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product. (h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

Subpart H–**Holding** and **Distribution** Sec. 211.142 **Warehousing** procedures. Written procedures describing the **warehousing** of drug products shall be established and followed. They shall include: (a) Quarantine of drug products before release by the quality control unit. (b) **Storage** of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

Subpart H–**Holding** and **Distribution** Sec. 211.150 **Distribution** procedures. Written procedures shall be established, and followed, describing the **Distribution** of drug products. They shall include: (a) A procedure whereby the oldest approved stock of

a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate. (b) A system by which the **Distribution** of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart J–Records and Reports Sec. 211.188 Batch production and control records. Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include: (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed; (b) Documentation that each significant step in the manufacture, processing, packing, or **holding** of the batch was accomplished, including: (1) Dates; (2) Identity of individual major equipment and lines used; (3) Specific identification of each batch of component or in-process material used; (4) Weights and measures of components used in the course of processing; (5) In-process and laboratory control results; (6) Inspection of the packaging and labeling area before and after use; (7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing; (8) Complete labeling control records, including specimens or copies of all labeling used; (9) Description of drug product containers and closures; (10) Any sampling performed; (11) Identification of the persons performing and directly supervising or checking each significant step in the operation; (12) Any investigation made according to Sec. 211.192. (13) Results of examinations made in accordance with Sec. 211.134.

Subpart J–Records and Reports Sec. 211.196 **Distribution** records. **Distribution** records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, **Distribution** records are not required to contain lot or control numbers.

Subpart K–Returned and Salvaged Drug Products Sec. 211.204 Returned drug products. Returned drug products shall be identified as such and **held**. If the conditions under which returned drug products have been **held, stored**, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of **storage** or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of Sec. 211.192. Procedures for the **holding**, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

# Appendix A-2

# Potential Formulary
## (Based on Current Use of Drugs Appropriate to Canadian Purchase)

ACCUPRIL
ACIPHEX
ACTONEL
ACTOS
ADVAIR DISKUS
AGGRENOX
ALLEGRA
ALLEGRA-D
ALPHAGAN-P
ALTACE
AMARYL
ARAVA
ARICEPT
ARIMIDEX
ARTHROTEC
ASACOL
ATROVENT
AVALIDE
AVANDIA
AVAPRO
BEXTRA
CASODEX
CELEBREX
CELEXA
CELLCEPT
CLARINEX
COMBIVENT
COMTAN
COREG
COSOPT OCUMETER PLUS
COZAAR
DETROL
DETROL LA
DIOVAN
DIOVAN HCT
EFFEXOR
EFFEXOR XR
ELMIRON
EVISTA
FEMARA
FLOMAX
FLONASE
FLOVENT
FOSAMAX
HUMALOG
HUMALOG MIX 75/25
HUMULIN
HYZAAR
IMITREX
INDERAL LA
LAMICTAL
LIPITOR
LUMIGAN
MIACALCIN
MOBIC
MONOPRIL
NASACORT
NASONEX
NEURONTIN
NEXIUM
NORVASC
PATANOL
PAXIL
PLAVIX
PRANDIN
PRAVACHOL
PREMARIN
PREMPRO
PREVACID
PROSCAR
PROTONIX
RHINOCORT AQUA
RISPERDAL
SEREVENT
SEROQUEL
SINGULAIR
STARLIX
TOPAMAX
TOPROL XL
TRAVATAN
TRICOR
URSO
VIOXX
WELLBUTRIN SR
XALATAN
ZETIA
ZOCOR
ZOFRAN
ZOLOFT
ZYPREXA
ZYRTEC
ZYRTEC-D

The prescription utilization data for the first nine months was annualized for purposes of cost comparison but not trended for increased utilization or price increases. Caremark estimates the total prescription drug spending for calendar year 2003; net of member co-payments at $226 million. The 232 selected line items account for 67% of that amount.

**Managed Care Plans**

State employees and retires participating in nine Managed Care plans had total prescription drug spending of $144 million during fiscal year 2003 (July 2002 – June 2003).

A detailed report listing expense by medication or line item is not available at the time of this report. Assumption was made to use the same percentage of expense for selected top brand name drugs as in the Caremark administered plan. This would amount to $96 million. Assuming the savings would be similar to the Caremark scenario, the savings in the managed care plans would be $37 million. The actual savings are likely to be higher since the co-payments in Managed Care plans are lower than the Caremark plan. Assuming an allowance of $1.3 million towards implementation of the Primary Care Pharmacist (PCPh) model, net savings potential for the limited number of drugs is $35.7 million. Additional data are required to project the employee and State portion of these savings.

The potential savings if all eligible prescriptions for employees and retirees in both plans are filled through Canadian pharmacies is estimated at $90.7 million. The variables include the exchange rate, drug price increase, and level of participation.

Realization of program savings is dependent on two main factors - which of the ten existing benefits plans could be moved to this type of program and how fast could the State effectively implement the program.

Assumptions necessary to complete the savings analysis have been obtained from Central Management Service for the nine managed care plans, Caremark, Inc. for the Quality Care Health Plan, and CanaRx (current vendor for the City of Springfield, MA program) for the estimated cost of the Canadian mail order program.

The assumed plan design for all ten plans under the Canadian Mail Order Program would be $0 co-payment for a three-month supply. The plan design and cost savings analysis assumes the employees and retirees would be required to pay shipping costs. We estimate the shipping cost to be approximately $12 per order and that would encourage the participants to consolidate multiple prescriptions in only one order per quarter.

**Cost Savings Projections**

<u>Quality Care Health Plan/Caremark Employees and Retirees</u>

The projected 12-month savings for this group is $55,000,000. This projection assumes all eligible prescriptions are filled in the Canadian Mail Order Plan. The variables include the currency exchange rate, manufacturer price increases, and level of employee/retiree participation. At an estimated participation rate of 33% of eligible prescriptions, the savings would be $18,300,000 for the first full year of Canadian Mail Order program.

Managed Care Employees and Retirees

The projected maximum 12-month savings for this group is $35,700,000. This projection assumes ALL eligible prescriptions are filled in the Canadian Mail Order Plan. The variables include the currency exchange rate, manufacturer price increases, and level of employee/retiree participation. At an estimated participation rate of 33% of eligible prescriptions the savings would be $11,900,000 for the first full year of Canadian Mail Order Plan.

Currently seven of the nine managed care contracts are funded by the State on a fully insured basis. The State pays each vendor a set premium on a monthly basis, which is negotiated as part of the annual contract renewal process. It is highly unlikely these contracts will be reopened by CMS prior to the annual renewal date. The implication is the State will not implement a Canadian Mail Order Plan for a majority of these managed care contracts until the next fiscal year.

# Appendix A-4

## Primary Care Pharmacist Model

**Concept:**

The multiplicity of drugs available and the complexities surrounding their safe and effective use make it necessary for organized health-care settings to have a sound program for maximizing rational drug use[1]. As the population ages, individuals are likely to be taking several medications for different chronic conditions. To be able to provide optimal benefit in a cost effective manner, we seek development of an enhanced ability for patients to consult with a qualified pharmacist on matters concerning their medication therapy.

**Proposal:**

Patients frequently have choice in seeing multiple physicians and may purchase prescriptions from different pharmacies and under different programs. These programs can vary under insured options, as well as by retail and mail order (domestic or non-domestic).

Increasingly, physicians in both managed care and fee for service domains are over-burdened and have scarce time and availability for patient inquiries on their prescription drugs.

The increasing complexity of drugs, as well as the vastly accelerating use of Direct to Consumer advertising by pharmaceutical companies is confusing to consumers of all ages, and not just seniors as frequently assumed.

Therefore, we are proposing development of a formalized role for Pharmacists in addressing these issues. This role would require additional instruction and certification by academic pharmacy institutions.

The Primary Care Pharmacist (PCPh) would be available to the Plan participants for inquiries, information and technical advice. Questions such as the appropriateness of generics vs. brand, anticipated or possible complications, and review of potential drug interactions, as well as patient-specific conditions and/or ethnicity all would be appropriate for the Primary Care Pharmacist.

The PCPh will be selected by the consumer, reimbursed by a fixed fee per prescription filled through mail order, and funded through the savings generated from the Canadian Mail Order Plan.

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[1] ASHP statement on the pharmacy and therapeutics committee. Am J Hosp Pharm. 1992; 49:2008–9.

## OTHER APPENDICES (ELECTRONIC OR COPIED TO BE ATTACHED)