3M | SoluPrep™ Brand

white paper

Quality of 3M Canada Skin Antiseptic Drug Products

3M™ SoluPrep™ 2% chlorhexidine gluconate (CHG) and 70% isopropyl alcohol (IPA)

Original March 2013
Revised June 2018

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White Paper—Quality of 3M Canada Skin Antiseptic Drug Products

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Executive Summary

Recent reports of intrinsic contamination of drug products, including skin antiseptics in the United States, have focused on the importance of strict adherence to established good manufacturing processes (GMP) and the application of quality assurance measures in the manufacture of drug products. FDA investigations and recalls[i, ii] associated with these events have prompted concern from the Canadian scientific community and healthcare workers regarding the need for sterile antiseptic products. Health Canada does not require that skin antiseptics intended for professional healthcare use be sterile and indeed some antiseptics such as chlorhexidine gluconate cannot withstand currently recognized terminal sterilization processes.

To protect patients and the public, Health Canada has established Good Manufacturing Practices Guidelines[iii] and a Guidance Document: Human-Use Antiseptic Drugs[iv] that outline the safety and efficacy requirements that manufacturers must achieve in order to meet the regulatory standards for licensure in Canada.

To our knowledge, 3M Canada is the only manufacturer at this time to have submitted the required clinical studies and received authorization for professional healthcare use antiseptic drug products. This authorization includes the 3M™ SoluPrep™ 2% CHG/70%IPA formulation.

To provide assurance to our valued customers on the quality of our skin antiseptics, 3M Canada has prepared this white paper that summarizes the routine measures we take to prevent contamination and avoid recalls. The white paper reviews the clinical efficacy studies and the quality control processes in place that guide the manufacture, packaging, microbial release testing, microbial out of specification and risk review investigation processes at 3M. The microbial testing and quality assurance processes implemented by 3M Canada exceed the requirements of both Health Canada and the FDA. The rigorous chemical and microbial standards employed to test both the raw ingredients and finished packaged products provide assurance that all batches of 3M™ SoluPrep™ 2%CHG/70%IPA skin antiseptic products are safe and analyzed as free from harmful contaminants at the time of release to our customers. It is 3M Canada's opinion that the rigorous processes described in this white paper support the quality, efficacy and safety of our 3M™ SoluPrep™ 2%CHG/70%IPA drug antiseptic products.

As an additional measure of assurance to our customers, 3M Canada requested an independent audit of our manufacturing processes and a review of the white paper by an internationally recognized expert, Dr. Michelle Alfa, who is a clinical microbiologist and professor at the University of Manitoba and principal investigator at the St. Boniface Research Centre. Dr. Alfa confirmed that the manufacturing and quality control processes in place at 3M Canada, and documented in the white paper, exceed published standards and ensure the 3M™ SoluPrep™ 2%CHG/70%IPA skin antiseptic products are safe for their intended use. Dr. Alfa's complete report is included in this 3M Canada white paper.

Footnotes

[i] http://www.fda.gov/Safety/Recalls/ucm239219.htm
[ii] http://fda.gov/Safety/Recalls/ucm247658.htm
[iii] Health Products and Food Branch Inspectorate. Good Manufacturing Practices (GMP) Guidelines – 2009 Ed. Version 2 (GUI-0001), March 4, 2011. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/compli-conform/gmp-bpf/docs/gui-0001-eng.pdf
[iv] Health Canada Guidance Document: Human-Use Antiseptic Drugs, Ottawa, 2009/11/27. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande guide-ld/antiseptic_guide_ld-eng.php

Report of independent audit
Dr. Michelle Alfa
March 17, 2013

Introduction

The recent Food and Drug Administration (FDA) action in the United States whereby there were initially product recalls and then ultimately closure of this single American facility has resulted in concerns within healthcare facilities in both the USA and Canada regarding the perceived need to have sterile antiseptic agents in healthcare. There is evidence to show that the alcohol prep pads manufactured by this one American facility were contaminated with *Bacillus cereus* that was linked to two invasive blood stream infections in children.[3] The shutdown of this facility by the FDA was a direct result of their failure to follow Good Manufacturing Procedures (GMP). Some of the key issues related to GMP gaps included but were not limited to

- problems with the "high quality" water used
- lack of a quality process to assess the microbial levels in the raw materials used
- lack of a quality process to assess the microbial levels in the final product
- lack of validation of the company's sterilization process for products labeled as sterile

Issues that healthcare providers are worried about

Most healthcare providers are unaware that antiseptic agents commonly used for skin preparation for line insertions etc., (e.g., alcohol, chlorhexidine-alcohol, povidone iodine, povidone iodine-alcohol prep pads) are not sold as "sterile" products. Furthermore, they are not aware that Health Canada does not require antiseptic agents to be "sterile." Healthcare providers worry that if the antiseptic agent is not "sterile" that it must be "contaminated" and is therefore not safe to use for skin preparation for invasive procedures.

Objective of the 3M white paper

A key objective of the 3M white paper is to provide information to healthcare providers to document the stringent quality process used by 3M Canada in the manufacture of their antiseptic agents. The key focus of the 3M white paper is on the various products sold in Canada that contain the widely used antiseptic agent 2% chlorhexidine gluconate/70% isopropyl alcohol (CHG-IPA). By outlining the quality process in the white paper, 3M Canada wants to demonstrate to healthcare providers that the quality process used by 3M Canada in the manufacture of CHG-IPA products goes beyond the current Canadian requirements set by Health Canada. The 3M white paper is expected to provide healthcare providers assurance that the CHG-IPA product is safe to use on patients for skin antisepsis despite not being sold as a "sterile" product.

3M™ SoluPrep™ 2% w/v CHG and 70% v/v IPA

outlining the quality process used by 3M Canada in the manufacture of CHG-IPA products

quality goes beyond the current requirements set by Health Canada

Dr. Alfa's mandate

In March 2012, I was asked by 3M Canada to provide an independent review of the 3M Canada white paper and document my expert opinion on the information provided.

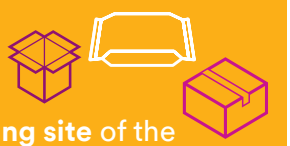
Michelle Alfa is a paid clinical and educational consultant to 3M Health Care.

Information and actions undertaken to meet this mandate

In order to meet this mandate, I performed an independent audit of the CHG-IPA manufacturing process used by 3M. This included on-site audits of the following facilities:

1. the **manufacturing site** of the CHG/IPA bulk solution

2. the **packaging site** of the Prep-Pad and various swabs containing CHG-IPA



3. the **analytical site** that does the microbiological testing of the bulk solution and final products

During these audits, I had extensive discussion with the staff of these facilities and was provided the testing standard operating procedures (SOPs), as well as the quality records documenting results of microbial testing from all three facilities.

In addition to the audits, I had extensive discussions with the staff at 3M Canada responsible for the development of the quality process that included what actions would be taken when any testing showed "Out Of Specification" (OOS) problems.

On Oct 4, 2012, I provided 3M Canada with a detailed report on my independent audit findings. In addition, I provided 3M Canada with my recommendations for clarification of the information provided in the 3M white paper. The following report contains my expert opinion on the materials provided in the 3M white paper (version June, 2018) and specifically on whether the antiseptic CHG-IPA preparations manufactured by 3M Canada are safe to use in healthcare to prepare skin for invasive procedures.

Comments on the 3M white paper

To provide expert opinion as a clinical microbiologist on the 3M white paper, I performed

1. A literature search to review the published evidence regarding contamination of antiseptic agents and the infections associated with such contamination.
2. A review of the current Canadian, America, and Australian guidelines regarding the manufacture of antiseptic agents.
3. A review of the Dec 12, 2012 FDA Public Hearing regarding the issue of contaminated antiseptic agents and whether "sterile" antiseptic agents should be required.
4. A review of the Feb 6, 2013 APIC position statement on whether "sterile" antiseptic agents should be required.
5. An independent audit of the 3M manufacturing process for CHG-IPA single-use applications.

It is clear from the new Health Canada Guidance Document on Human-use Antiseptic Drugs[6] (effective Dec 3, 2009) that in Canada the manufacture and sale of antiseptic agents for use in healthcare have different classifications and different regulatory requirements from antiseptic agents used outside of healthcare. Specifically, antiseptic agents including benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chloroxylenol, methylbenzethonium chloride, peracetic acid, triclocarban and triclosan, whether used alone or as mixtures with other ingredients, are now classified as "drugs" and are regulated as pharmaceutical products by the Food and Drugs Act.

As part of this reclassification, antiseptic agents used in healthcare must follow the *in vitro* and *in vivo* testing protocols, as well as the labelling requirements that are outlined in the Health Canada Guidance Document.[6] This testing is designed to ensure that the antiseptic agent has adequate microbial killing ability using standardized protocols and test organisms. In addition the manufacture of antiseptic agents must comply with Good Manufacturing Procedures (GMP) as defined by the Health Products and Food Branch Inspectorate, Health Canada.[7] This GMP process includes drug and health product regulations indicating that facilities that fabricate, package, or label antiseptic agents used in healthcare must have Health Canada inspections performed every two years to document that the manufacturing process is adequate (POL-0011).[4]

There is no requirement in the Health Canada Guidance Document[6] that human-use antiseptic drugs must be sterile. This guidance document[6] indicates that for purified water used in the production of antiseptic agents that there should be < 100 cfu/mL and an absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* for cutaneous preparations. The Health Canada regulations[6] do indicate that if a manufacturer labels their antiseptic agent as "sterile" then additional testing requirements for sterility claims are needed. The USP <1111> requirements[9] for non-sterile products indicates that for cutaneous use, there should be < 100 cfu/mL for the total aerobic microbial count and < 10 cfu/mL for the total yeast and moulds count and that there should be no *S. aureus* and no *P. aeruginosa* per 1 g or 1 mL of product. The Australian guidelines[2] have additional requirements beyond those stated in Canada[6] and the USA[9] in that the total aerobic microbial count should be < 10 cfu/mL and there should be no *Pseudomonads* (i.e. not limited to *P. aeruginosa* only).

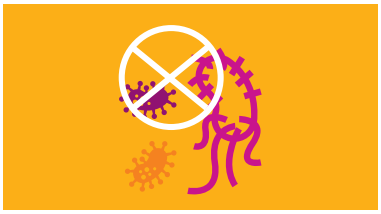
It is clear from the 3M Canada white paper (Table 1) that the requirements used by 3M Canada consist of a composite of the most stringent cutoffs from all three countries.

The audit I performed of the manufacturing process used by 3M Canada to produce the CHG-IPA skin prep products demonstrated compliance with Health Canada's GMP Guidelines (GUI-0001)[7] as well as GMP Inspection Policy for Canadian Drug Establishments (POL-0011).[4] The process outlined in the 3M Canada white paper, the Appendix reflects what I observed during the audit in that appropriate microbial testing is performed on the raw materials as well as the finished product. Furthermore, the data I reviewed during the audit and through subsequent discussion with 3M staff confirmed that detection of **any organism,** even if only found at 1 cfu/mL to 10 cfu/mL (although acceptable in an antiseptic drug) would still result in a thorough risk review process. This has been reflected on Page 15, of this document.

There has been recent concern in healthcare that if CHG-IPA is not a "sterile" product that this increases the risk of infections in patients from intrinsic contaminants that may be in the antiseptic agent at low levels. The FDA hearings[5] allowed for in-depth discussion and expert input on the need for sterile skin antiseptic agents. The experts who testified indicated that currently there is no way to adequately provide chlorhexidine gluconate (CHG) or povidone iodine (PI) based antiseptic agent solutions that are sterile (it is possible to provide sterile applicators, but the antiseptic liquid that may be present in a sealed vial along with the sterile applicator cannot be sterilized) as the traditional sterilization processes for liquids (e.g. steam, irradiation etc.,) cause the CHG and PI component in the antiseptic solutions to deteriorate. It was clear from the public hearing that although it may seem ideal to have "sterile" antiseptic agents, in actuality there is little added safety to be gained compared to the current situation providing the manufacturing process is controlled to ensure the final product does not have unacceptable microbial levels.

Indeed, the two main messages from this FDA hearing[5] were

1 **Skin antisepsis agents should be packaged as ready-to-use, single-use preparations** as this would reduce the risk of accidental contamination related to diluting with contaminated water and "topping up" problems associated with extended use of larger volumes of antiseptic agents.



2 **The manufacturing process should be more stringently controlled** and adequate testing should be performed to prevent the release of antiseptic products that have intrinsic contamination with **any** organism above the accepted cutoffs.

The Association for Professionals in Infection Control and Epidemiology (APIC) response[1] (Feb 13, 2013) to the FDA public hearings in Dec 2012 indicated that APIC recommends that antiseptic agents used for prepping the skin for invasive procedures should be provided as sterile products.

This position is reflected by their statement:

> *APIC believes that all skin preparation products should be manufactured to be sterile. While we are aware that research and work needs to be done to enable the production of sterile prep agents, APIC believes the time has come to begin those processes to provide sterile prep products.*

Despite this recommendation by APIC,[1] it is clear from the FDA Public Hearings[5] that there is a lack of published data demonstrating that the use of sterile antiseptic agents for skin prep for invasive procedures would significantly reduce the risk of infections from invasive procedures. In addition, there is published evidence that there is substantial bacillus contamination of the high-touch areas in healthcare (25 of 35 sites tested) and that this ubiquitous presence of bacillus spores is thought to contribute to contamination of blood culture collection.[8] The clinical review performed in this study indicated that only 4% of the 133 blood cultures growing Bacillus species were considered to be true infections (92% deemed contamination or probable contamination, and 4% of unknown status).[8] This data indicates that independent of any intrinsic contamination of antiseptic agents with bacillus spores, it is important to recognize that there is a high risk of bacillus spores being introduced from accidental environmental contamination during an invasive procedure.

The APIC response[1] also endorsed single-use dosing formats for antiseptic agents and supported the need for more stringent manufacturing quality processes as reflected in their statement:

> *There needs to be a critical look at these testing criteria for manufacturers followed by development of enhanced requirements to cover the recurring contaminating organism culprits as well as the resistant organisms of great concern in healthcare today.*

Reviewing the published literature to date[3,8,10] as well as the FDA transcript docket[5] of the public hearings held in December 2012 on this issue has further solidified my expert opinion that the CHG-IPA products manufactured by 3M Canada are safe for their intended use. **The combined CHG-IPA product is not one of the products that was part of the FDA recalls**[5] (the recalls included ethanol prep pads and povidone iodine products). Indeed there has been no published data (that I am aware of) indicating that there have been any intrinsically contaminated CHG-IPA skin antiseptic products.[3,5,10] Furthermore, the current microbial testing as part of the quality process requirements used by **3M surpasses the requirements of both Health Canada[6] and the FDA[9] in that detection of any organisms in CHG-IPA final product** (even if below the acceptable level for non-sterile product) results in a full risk review that must conclusively establish the safety of the lot before it is released to market. Furthermore, there is 3M data that indicates that the CHG-IPA product over a number of days is capable of killing *Geobacillus stearothermophilus* and *Bacillus atrophaeus* spores. This provides an added level of assurance that the final packaged CHG-IPA product is safe for its intended use.

Conclusions

It is my expert opinion that the information provided in the 3M Canada white paper accurately reflects the processes used by 3M Canada in the manufacture and testing of their CHG-IPA products. Furthermore, it is my expert opinion that the manufacturing process and microbial testing and quality systems that are in place at 3M Canada do ensure a safe product for the intended use of the CHG-IPA products that are sold in Canada. In addition, I support the APIC[1] and FDA public hearing[5] recommendations that regardless of whether an antiseptic agent is "sterile" or "not sterile, but manufactured using stringently controlled processes," there is a need for more education to ensure appropriate clinical application of antiseptic agents.

In my expert opinion, the 3M Canada white paper is a valuable resource for Canadian healthcare facilities as it clarifies the stringency of microbial testing of 3M Canada's CHG-IPA products and highlights the issues related to appropriate clinical application of antiseptic agents.

References

[1] APIC Comments to FDA on Antiseptic Patient Preoperative Skin Preparation Products Docket No. FDA-2012-N-1040. (APIC response letter dated Feb 6, 2013).

[2] Australian Regulatory Guidelines for Prescription Medicines, Appendix 17: Microbial quality of medicines; http://www.tga.gov.au/pdf/pm-argpm-ap17.pdf

[3] Dolan SA, Littlehorn C, Glode MP, Dowell E, Xavier K, Nyquist AC, Todd JK. Association of Bacillus cereus infection with contaminated Alcohol Prep Pads. Infection Control and Hospital Epidemiology 2012;33:7.

[4] Drugs and Health Products: GMP Inspection Policy for Canadian Drug Establishments (POL-0011) Last modified 2008-01-31.

[5] FDA Transcript: Docket No: FDA-2012-N-1040 Antiseptic Patient Pre-operative skin Preparation Products. Public Hearing Dec 12, 2012.

[6] Guidance Document: Human-Use Antiseptic Drugs. Nov 27, 2009. Health Canada Publisher, Ottawa, Ontario.

[7] Health Products and food Branch Inspectorate: Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2. Health Canada Publisher, Ottawa, Ontario.

[8] Meites E, Taur Y, Marino L, Schaefer M, Eagen J, Jensen B, Williams M, Kamboj M, Srinivasan A. Investigation of increased rates of isolation of Bacillus species. Infection Control and Hospital Epidemiology 2010: 31:1257-1263.

[9] USP<1111> Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.

[10] Weber JD, Rutala WA Sickbert-Bennett EE. Outbreaks associated with contaminated antiseptics and disinfectants. Antimicrobial Agents and Chemotherapy 2007;51:4217-4224.

White Paper by 3M Canada

Quality Processes for Skin Antiseptic Solutions

3M™ SoluPrep™ 2% w/v chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA)

Introduction

It is well recognized that many healthcare-associated infections such as bloodstream and surgical site infections can result from microorganisms that are found on patient's skin. Ensuring effective skin antisepsis prior to the performance of invasive procedures that puncture the skin is a critical infection prevention measure. To protect patients and the public, Health Canada has developed a Guidance Document: Human-Use Antiseptic Drugs[1] that outlines the safety and efficacy requirements that must be achieved by manufacturers in order to meet the regulatory standards for licensure in Canada. Health Canada considers a skin antiseptic agent to be one that

> *inactivates, reduces, prevents or arrests growth of microorganisms with the inherent intent to mitigate or prevent disease.*[1]

Skin antiseptics licensed for use in Canadian healthcare facilities must meet even more rigorous regulatory standards in order to be authorized as professional healthcare use products. This rigour provides optimum protection for patients who are exposed to high-risk environments and organisms, and for whom the risk of infection is highest. The safety and efficacy requirements are outlined in section 3.1.4 of the Guidance Document.[1] 3M Canada is the first manufacturer to have submitted supporting clinical studies and received Health Canada authorization in accordance to the Professional Healthcare Use Pre-operative Skin Preparation classification.

Health Canada does not require that skin antiseptics intended for professional healthcare use be sterile. However, as stated in section 4.1.3 of the Guidance Document, "Additional supporting data may be required to support the quality of the finished antiseptic product."[1]

Although uncommon, instances of contaminated skin antiseptics have been reported.[2,3] In a review of outbreaks and pseudo-outbreaks conducted by Weber et al.[3] where intrinsic contamination was identified, contaminated water was most frequently found to be the source. Weber describes instances of contamination of the following antiseptic solutions: alcohol, povidone iodine, chlorhexidine, benzalkonium chloride, triclosan, chloroxylenol, and chlorhexidine/cetrimide. In the preparation of this white paper, a thorough literature search was conducted and there was no peer-reviewed report of contamination in a combined solution of chlorhexidine gluconate (CHG)/isopropyl alcohol (IPA) found.

A recent investigation in Colorado into an increased incidence of blood cultures positive for *Bacillus cereus* and two invasive infections in children resulted in the identification of *Bacillus cereus* contamination of alcohol prep pads manufactured at a single facility in the United States.[2] Mandatory state reporting of this event resulted in a U.S. Food and Drug Administration (FDA) investigation and eventually an international recall of all lots of alcohol prep pads manufactured by the identified company.[4] This was followed shortly thereafter by a second voluntary recall by the same manufacturer due to bacterial contamination of povidone iodine prep pads with *Elizabethkingia meningoseptica*.[5] After inspections of the facility, authorities from the FDA reported concerns with adherence to Good Manufacturing Procedures (GMP). A non-exhaustive list reported the following concerns:

- Sterilization processes were not validated;
- Investigation suggested that raw materials used in other similar products were the source of contamination;
- Lack of a quality assurance process for microbial testing at the time of product release;
- Problems identified with the company's "high purity" water system, including leaks, failing drains that could result in sewage backup, problems with the sanitation and a lack of recordkeeping regarding the water system.

In summary, basic GMPs were not followed and a lack of thorough processes to control the quality of drug products resulted in the U.S. Marshals ordering a facility shutdown after the company failed to comply with an earlier U.S. FDA request to close voluntarily.

These recent recalls and investigations of the FDA related to intrinsic microbial contamination have prompted concern from the Canadian scientific community and healthcare workers regarding the need for sterile antiseptic drug products. **To our knowledge, there is no single-use applicator of 2% CHG/70% IPA skin antiseptic in Canada in which the chlorhexidine gluconate solution is sterile.**

In order to be proactive and provide assurance to our valued customers, 3M Canada has prepared this white paper to summarize the routine measures we take to prevent contamination and avoid recalls such as those described above. It is 3M Canada's opinion that the rigorous manufacturing, packaging and internal control processes described in this document support the quality, efficacy and safety of our 3M™ SoluPrep™ 2% CHG/70% IPA drug products for their intended use.

3M Canada Drug Products

Effective reduction of the bacterial load on the patient's skin through the use of topical antiseptics is an important part of the preparation before invasive medical and surgical procedures. The indications for 3M Canada skin antiseptic products are :

Combination drug products containing CHG/IPA are used extensively in many countries because they are well recognized as fast-acting antiseptics (due to the alcohol) that exhibit long-lasting persistent activity (due to the chlorhexidine gluconate). They are effective against Gram-positive and Gram-negative bacteria, fungi and viruses.

Published evidence-based guidelines and practice standards recommend the use of chlorhexidine gluconate skin antiseptics for the prevention of infections associated with invasive medical procedures.[6,7,8] Solutions combining CHG and IPA are increasingly considered the drug products of choice given the substantial evidence in the published literature. The combination of CHG and IPA has been shown to be highly effective in reducing both surgical site and intravascular catheter-related infections.[9,10] The excellent persistent activity provided by CHG is of particular importance in preventing infections when it is used to prepare skin in situations where invasive devices are left in place, such as at intravascular catheter sites.

The development and design of all 3M Canada drug product packaging configurations to take into account the following important points:

- A barrier to maintain potency of the active ingredients,
- A barrier to prevent microbial contamination,
- A barrier to avoid degradation of the drug solution and,
- A compatible applicator that will not compromise the integrity of the patient's skin.

Good Manufacturing Practices (GMP)[11]

Good Manufacturing Practices guidelines apply to

pharmaceutical **radiopharmaceutical** **biological** **and veterinary drugs...**

...and were developed by Health Canada in consultation with stakeholders. The guidelines pertain to Division 2, Part C of Canada's Food and Drug Regulations and must be followed by all manufacturers of drug products (including antiseptics) to support the safety and quality of finished drug products. These guidelines include

- the premises
- equipment
- personnel
- raw material testing
- manufacturing control
- quality control

In addition, the guidelines include a stability requirement to support the quality, efficacy and safety of a drug product through its entire shelf life. An important measure in preventing microbial contamination of drug products is a sound cleaning and sanitization program for the controlled environments used in the manufacture of pharmaceutical products. During production, drug products may be exposed to contamination from pharmaceutical ingredients, process water, packaging components, the manufacturing environment, processing equipment, and manufacturing operators. Good Manufacturing Practices dictate the size, design, construction, and location of buildings and construction materials, and the appropriate material flow to facilitate cleaning, maintenance, and proper operations for the manufacture of drug products. The cleaning and sanitization program must achieve specified cleanliness standards, control microbial contamination of products, and be designed to prevent the chemical contamination of pharmaceutical ingredients, product-contact surfaces and/or equipment, packaging materials and ultimately the drug products. These requirements also apply to non-sterile dosage forms where the microbial contamination is controlled by the selection of appropriate pharmaceutical ingredients, utilities, manufacturing environments, comprehensive equipment cleaning procedures, quality control measures to ensure water quality is acceptable and inclusion of suitable preservatives and product packaging design. From these requirements, it is clear that compliant products must meet rigorous standards.

These activities would be without meaning in the absence of good quality control (QC) systems that monitor each step of the manufacturing/packaging process. The closing of the U.S. facility described previously is an example of actions resulting from ineffective quality control mechanisms. 3M Canada performs regular internal audits of the entire manufacturing/packaging processes. In addition, Health Canada inspectors perform regular inspections of our facilities to ensure compliance to the standards established in their guidance document.

Clinical Efficacy Study

3M Canada has developed and implemented an extensive clinical program for its antiseptic drug products based on the recommendations established in the Guidance Document: Human-Use Antiseptic Drugs, 2009/11/27.[1] According to this document, products approved for Professional Healthcare Use are intended to "reduce transient and/or resident organisms on skin in a healthcare setting." Supporting efficacy data that includes demonstration of 6 hours' persistence must be submitted and approved.

For all of the chlorhexidine gluconate drug products, 3M Canada has conducted *in vivo* efficacy studies according to ASTM E 1173 Standard Test Method for Evaluation of a Preoperative, Pre-catheterization, or Pre-injection Skin Preparation. Additionally, *in vitro* efficacy studies according to EN13727 Chemical disinfectants and antiseptics—Quantitative suspension test for the evaluation of bactericidal activity of chemical disinfectants for instruments used in the medical area—Test method and requirements (phase 2, step 1) listed in the aforementioned guidance document have been completed.

3M Canada strongly encourages all healthcare professionals to request that manufacturers provide efficacy data for all antiseptic drug products used in their hospitals to ensure products meet the current Health Canada requirements as described in the guidance document.

In addition to the Health Canada required testing, 3M Canada has performed additional studies to assess the efficacy of our skin antiseptic products under various conditions, including a study that demonstrated the sporicidal capability of 3M™ SoluPrep™ 2% CHG/70% IPA solution to kill *Geobacillus stearothermophilus* and *Bacillus atrophaeus* spores in a packaged finished product at room temperature.[12]

Quality Control (QC)

All 3M Canada drug products released to the market have undergone extensive QC testing during manufacturing of the drug solutions as well as during packaging of the finished drug products (see Appendix for a detailed overview of the process).

QC testing during manufacturing of the drug solutions

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QC testing during packaging of the finished drug products

Manufacturing

Following confirmation that all ingredients have met test specifications, the batch is released and the bulk intermediate solution is filtered and transferred to holding tanks in preparation for the packaging phase of the manufacturing process. The purified water used in the manufacture of our drug products comes from a validated water system. The purified water used during the bulk manufacturing is tested daily for conductivity and total organic carbon (TOC) levels and tested weekly for microbial levels. The limits for these tests are in accordance with U.S. Pharmacopeia (USP) requirements.[13]

Packaging

The packaging process is conducted in controlled environments that exceed the physical requirements of GMP described previously in this document (see Good Manufacturing Practices, pg. 13). A non-exhaustive list of the QC tests comprises visual checks (dimensions, labels, print colour, lot number, presence of applicator), a vacuum test and weight checks every hour.

Microbial Release Testing

Patient safety and the manufacture of high quality and safe products are a priority for the company. 3M Canada has developed state-of-the-art, validated analytical methods that are used for all antiseptic product testing. The release specifications of the drug products are designed to ensure the safety and efficacy of each manufactured batch before it is made available for use.

The microbial limit methods are qualified to demonstrate that the microbial enumeration tests, as well as tests for specified microorganisms, are suitable for bulk intermediate solutions and finished drug products containing CHG and IPA. The microbial testing specifications not only meet the USP[15] requirements for pharmaceutical products for cutaneous use but also exceed the more stringent Therapeutic Goods Administration (TGA)[14] (Australia) requirements for microbial count limits.

- The 3M specification limit for microbial testing on finished products is ≤ 10 cfu/mL, for the **sum** of total aerobic microbial count (TAMC) and total yeasts and moulds count (TYMC). This specification limit is more stringent than the USP specification of ≤ 100 cfu/mL for TAMC **and** ≤ 10 cfu/mL for TYMC.
- In addition to the ≤ 10 cfu/mL limit, the 3M specification requires that **growth of any organism detected between 1 cfu/mL and 10 cfu/mL is identified and subjected to a thorough risk review process.** The risk review will determine the disposition of the lot.
- In addition to USP requirements and according to TGA requirements, the absence of all pseudomonads must be observed.

Table 1: Summary of Acceptance Criteria for Antiseptics Microbial Limit Tests

Test	3M Finished Product	USP Nonsterile Dosage Forms (Cutaneous Use)[15]	TGA Nonsterile Dosage Forms (Cutaneous Use and Antiseptics)[14]
Total aerobic microbial count (TAMC)	Sum of TAMC and TYMC ≤ 10 cfu/mL (if any growth detected, perform identification and investigation)	≤ 100 cfu/mL	≤ 10 cfu/mL
Total yeasts and moulds count (TYMC)		≤ 10 cfu/mL	Same as USP
Staphylococcus aureus detection	Absent	Absent	Same as USP
Pseudomonas aeruginosa detection	Absent	Absent	Same as USP
Pseudomonads detection	Absent (if presence observed, perform identification and investigation)	Not specified	Absent

Microbial Out-of-Specification (OOS) and Risk Review Investigation Process

3M Canada's standard for all skin antiseptic products is that no growth will be detected. This is supported by a comprehensive out of specification investigation process for the laboratories that perform microbial testing on the skin antiseptic products. The process ensures that laboratory investigation reports deliver critical data to support a multi-disciplinary team (manufacturing, medical, microbiology, quality, R&D and regulatory) approach to quality investigation reports (QIR) and risk reviews.

A result is considered to be out of specification when any microorganism is recovered above the specified level, 10 cfu/mL. If the growth detected is above this finished product specification limit the product is not released to the market. The OOS protocol is in place to ensure that only safe product is released to the market.

In addition to the out of specification protocol, growth of any microorganism at a level lower than the specification limit of 10 cfu/mL (between 1 – 10 cfu/mL) initiates a formal risk review investigation process. The risk review process includes, but is not limited to, identification of the organism, repeat testing, scientific and medical literature review, performance of studies using the antiseptic solution and the microorganism found, and a formal assessment and approval process by our medical, technical, regulatory and quality personnel. The risk review process must conclusively establish that the product is safe for use in healthcare to prepare skin for invasive procedures and is free from harmful contaminants before the finished product can be released to the market.

Clinical Application

This white paper describes the rigorous quality assurance processes to which the manufacture and release of 3M Canada skin antiseptic products adhere and that allow us to provide assurance to customers that our products are manufactured in accordance with Good Manufacturing Practices (GMP) and determined safe for use. In clinical care settings it is equally important that skin antiseptics are applied in a manner that does not introduce contamination. 3M Canada packages 3M™ SoluPrep™ 2% CHG/70% IPA skin antiseptics in volumes and formats designed for application within the operating room environment and for additional healthcare settings where invasive medical and surgical procedures may be performed.

Operating room standards[16,17] have determined that best practice for applying skin antiseptics prior to a surgical procedure includes having a non-scrubbed individual apply the antiseptic. This is intended to reduce the risk of contamination that is considered to be high when a scrubbed individual performs the skin preparation. 3M Canada supports this practice standard for operating room settings.

There are many invasive medical procedures performed outside the controlled and "sterile" environment of the operating room that require the use of skin antiseptics. These can be simple procedures such as peripheral venipunctures that pose a low risk of infection or procedures where the infection risk is high such as insertion of a central venous catheter. The complexity of sterile technique applied to perform these procedures will vary. Accordingly, a simple no-touch technique application of the antiseptic may suffice or the adoption of more stringent operating room practices may be required.

Application Example

Insertion of a Central Venous Catheter

The application of skin antiseptic prior to the insertion of a sterile central venous catheter is an example of a "surgical" procedure that carries a high risk of contamination and infection and is often performed in the higher-risk environment at the patient bedside. 3M Canada recommends the adoption of the operating room best practice standard, having a non-scrubbed worker apply the skin antiseptic[16,17] prior to the insertion of a sterile central venous catheter. Compliance with this best practice recommendation will help prevent contamination of the sterile gown when standing at the patient bedside and reaching over a non-sterile and non-draped area.

An added benefit of this recommendation is that the skin antiseptic is allowed sufficient time to completely air dry prior to the performance of the procedure. Thorough drying of the skin antiseptic optimizes efficacy of the solution and dressing adhesion while reducing the potential for skin irritation that can occur when dressings are applied to skin that is not dry.

Application Example

Maintenance Care, Central Venous Catheter *in situ*

Skin antiseptics are also required to cleanse the skin at the site of an existing intravascular catheter in conjunction with a dressing change procedure. Because resident bacteria are found within the layers of the skin and are known to repopulate the skin over time even when skin is protected by a sterile dressing,[18] neither the skin at the insertion site nor the portion of the line that has been in contact with the skin is by definition sterile. During the performance of this procedure, it is of utmost importance that asepsis be maintained so that microorganisms are not introduced by the healthcare worker. In most cases, the application of skin antiseptics during maintenance care is performed using a no-touch technique.

Sometimes during the performance of a dressing change, it may be necessary to contact the skin near the central line insertion site with sterile gloves in order to apply a securement device. In this situation, the gloved hands are exposed to the applicator and the antiseptic solution. It is important to recognize that 3M skin antiseptic solutions have been manufactured and packaged according to GMP and have met the stringent microbial release testing procedures identified in this paper. In addition, the applicator has been packaged immersed in the CHG/IPA solution and internal studies have demonstrated the capability of 3M™ SoluPrep™ 2% CHG/70%IPA solution to kill *Geobacillus stearothermophilus* and *Bacillus atrophaeus* spores in a packaged finished product. In the practice scenario described, and assuming the worker has maintained aseptic technique, contact between the applicator and the sterile gloves exposes the gloves to the same solution that has previously been applied directly to the patient's skin at the central line insertion site. It is our opinion that handling the applicator and CHG/IPA solution in such a manner maintains asepsis and minimizes risk by not introducing additional organisms that may be considered harmful to patients.

Conclusions

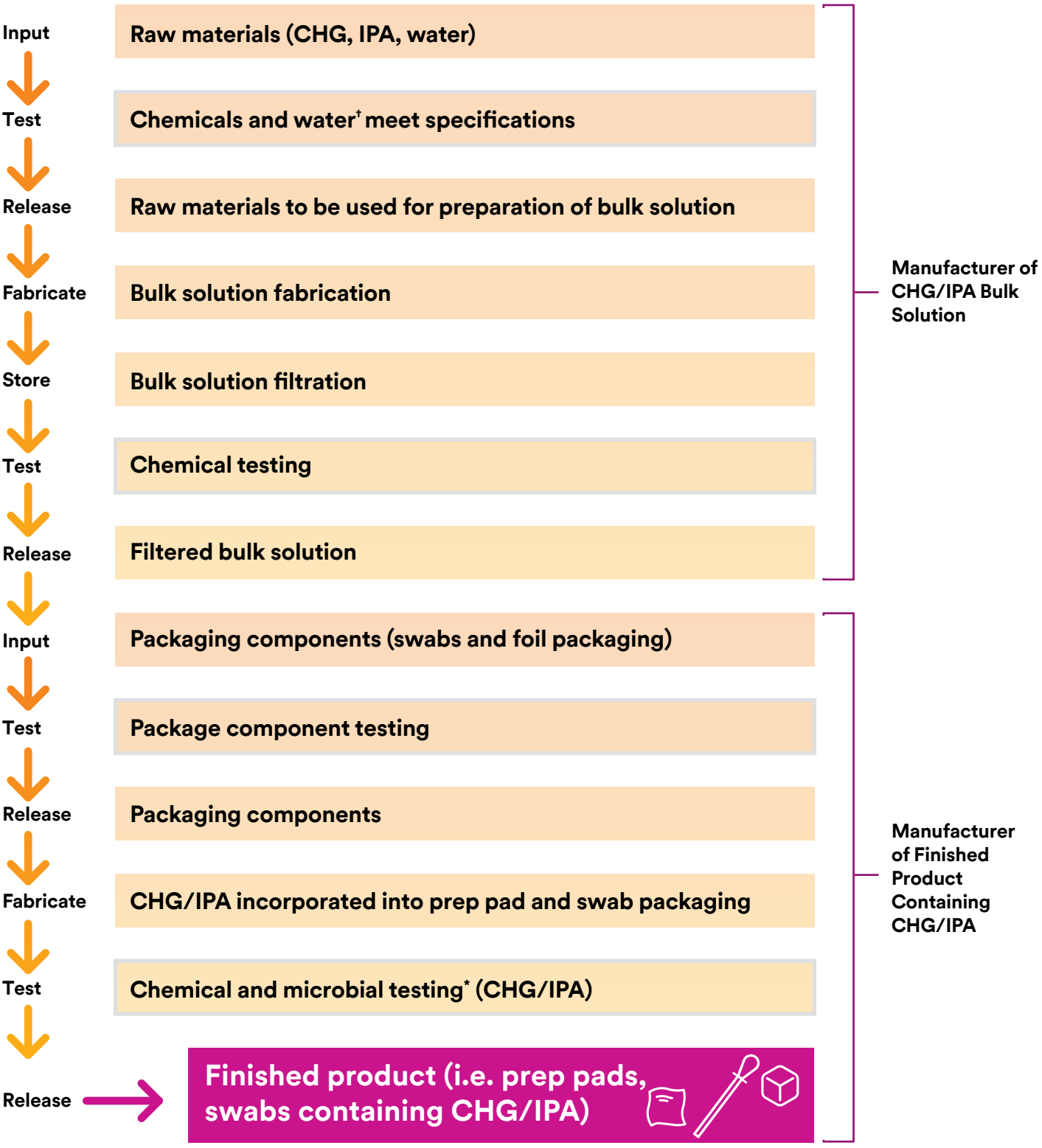
3M Canada chlorhexidine gluconate skin antiseptic drug products (including 3M™ SoluPrep™ 2% CHG/70% IPA) have been available to the Canadian healthcare market since 2002. During this time, over 1 billion patient applications have been performed. 3M Canada is proud to report that no harmful microorganisms have ever been recovered within our level of detection (≥ 1 cfu/mL) from any finished CHG/IPA skin antiseptic products.

3M™ SoluPrep™ 2% CHG/70% IPA skin antiseptic solutions are not "sterile" products. It is recognized that antiseptic ingredients such as chlorhexidine gluconate degrade when exposed to currently recognized methods used for terminal sterilization.[19] The excellent quality assurance measures outlined in this white paper and used by 3M throughout the manufacturing and packaging processes have been designed to exceed Health Canada requirements and ensure the quality and safety of 3M drug products intended for use in healthcare settings prior to invasive procedures. The rigorous chemical and microbial standards established to test both the raw ingredients and finished products provide assurance that all batches of 3M™ SoluPrep™ 2% CHG/70% IPA skin antiseptic products are safe and analyzed as free from harmful contaminants at the time of release to our customers.

Internal testing that demonstrates the capability of 3M™ SoluPrep™ 2%CHG/70%IPA solution to kill *Geobacillus stearothermophilus* and *Bacillus atrophaeus* spores in a packaged finished product provides an additional level of assurance of the microbial safety of this product to customers.

Appendix

3M Manufacturing and Packaging Quality Control Flow Chart



†The purified water used in the manufacture of either CHG/IPA or CHG-aqueous is tested weekly for microbial levels to ensure it complies with U.S. Pharmacopeia (USP) requirements.
*Samples sent to testing laboratory for microbial testing

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