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MINNESOTA BOARD OF PHARMACY

Report on a study to determine the appropriateness and feasibility of requiring mail order and specialty pharmacies to enclose in each medication's packaging a method by which the patient can easily detect improper storage or temperature variations.

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COST OF REPORT

Minnesota Statutes §3.197 states that a "report to the legislature must contain, at the beginning of the report, the cost of preparing the report, including any costs incurred by another agency or another level of government". The estimated cost of preparing this report was **$3,000.00**. That is the approximate value, in terms of salary and benefits, of the time that Board staff spent on preparing the report.

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INTRODUCTION

2021 Minn. Laws 1st Spl. Sess. Chap. 7 Art. 5 Sec. 5 states that the Board of Pharmacy must "conduct a study to determine the appropriateness and feasibility of requiring mail order and specialty pharmacies to enclose in each medication's packaging a method by which the patient can easily detect improper storage or temperature variations that may have occurred during the delivery of a medication. The board shall report the results of the study by January 15, 2022, to the chairs and ranking minority members of the legislative committees with jurisdiction over health finance and policy."

Questions to be answered:

1. Would placing temperature monitoring devices in shipping containers be effective?
2. The pharmacy benefit management companies (PBMs) claim the cheaper devices have a lot of false positives and false negatives – and the more accurate ones are very expensive. Are there studies to substantiate this claim.
3. The PBMs claim the most important thing is to have good policies and procedures in place – and to test their shipping methods. Is there support for that argument?

I. Background

Extreme temperatures can degrade medications, potentially rendering them unsafe or ineffective for patients. Industry guidelines make clear that pharmacies should package and ship medications in accordance with their recommended temperature range. There are numerous pharmaceutical temperature monitoring devices available that are designed to signal when a shipped medication has been exposed to temperatures outside of their recommended range. These devices range from simple inexpensive temperature monitoring tags averaging $1.99 per tag to more sophisticated reusable temperature monitoring data loggers priced well over $100 per device. This study was primarily concerned with the feasibility and reliability of the disposable temperature indicator tags.

Temperature indicator tags are designed to change color when a temperature excursion has occurred. They detect and reflect an excursion that occurred at a point in time during transport. While they are able to indicate that an excursion has occurred, most do not indicate the length of time the product was exposed to the temperature out of range. However, some tags are designed to indicate excursion time as a range. For example, WarmMark temp tag is a single-use, ascending time and temperature indicator that changes color when temperatures warm to a specified threshold, but also indicates whether exposure to that duration is brief (> 1 hour), medium (>3 hours), or prolonged (>12 hours) based on that sensor's specific temperature threshold. The cost is approximately $2 per tag.

While the manufacturers of these indicator tags claim they are highly accurate, currently there are no published studies assessing the number of false-positive or false-negative readings when included in the packaging and shipping of medications. Therefore, this study was not able to determine the reliability of using temperature indicator tags.

II. Available Studies

As previously mentioned, there are no studies looking specifically at the reliability of temperature indicator tags. Furthermore, there are very few studies available on the topic in general. Most studies only confirm that a problem with temperature excursions exist. However, one study from 2014, sponsored by Temptime Corporation, manufacturers of the TransTracker F temperature monitoring tag, evaluated whether including a

TransTracker F visual heat indicator tag could reduce costs and increase patient satisfaction when included in specialty pharmaceutical shipments.

In the study, five (5) specialty pharmacies agreed to include a TransTracker F visual heat indicator, a single-use device that monitors temperature exposures during shipping and signals to show when a specific temperature has been exceeded for a defined time period (2 hours). The patient was also provided a letter explaining the study as well as a survey form. Specialty pharmacies from the Northeast, Southeast, Midwest, Western regions participated, and 5,967 patient responses were returned. The study began in 2012 and results are reported through 12/31/13.

Results of the survey demonstrated positive customer satisfaction. Over 95% of patients agree that a temperature indicator included with shipments would increase their confidence and that including a visual indicator with each shipment of medicines to patients shows a concern for their safety. Also, if given the choice, 89% of participants would choose to receive medicine from a company that includes a visual temperature indicator in every shipment versus a company that did not. An overwhelming majority of patients – 97% – want the company that sends medicine to them to include a TransTracker® F temperature indicator in the box whenever medicines are shipped to them.

However, the incidence of indicators that changed color alerting patients of the potential for heat damage occurred in less than 2% of shipments (1.5%). Based on this study, there is no way to determine if the 1.5% of alerts were reliable (no false positive or false-negative readings), only that the indicator tag turned color (indicating an excursion occurred).

The White Paper can be found at:
http://www.samedanltd.com/uploads/pdf/white_paper/ba838e396a49d883670166080afaa693.pdf

III. Shipping Practices

I spoke with John Sisto, an industry expert with Express Scripts, to gain his perspective on the use of temperature indicator tags. Mr. Sisto states that indicator tags identify the problem after the fact rather than preventing the problem from occurring. He views the tags as not useful stating that they reflect a "moment in time" but do not provide information about the length of time the drug product was exposed to temperatures out of recommended range. He says the focus should be cold chain integrity and the importance of validating the pharmacy's shipping processes and packaging. **Independent testing** to test packaging should be a requirement. This test should validate the type of carton, insulation, cooler, gel pack, etc. and prove mathematically that the packaging was sufficient to maintain proper temperature through the shipment process in all types of weather.

The importance of cold chain management is recognized by specialty pharmacy accreditation bodies, including the Utilization Review Accreditation Commission (URAC) and the Accreditation Commission for Health Care (ACHC). For cold chain distribution standards, URAC requires criteria for selecting modes of transit and packaging products, and requires a validated distribution process with controls that address:

- Initial testing procedures for packaging products
- Using the correct packaging products
- Following established packing instructions
- Maintaining manufacturers' storage requirements
- A method to determine if shipments should be purposely held
- A plan to handle products in case of a breakdown in the distribution process

URAC 4.0, announced at the end of 2019, expands on previous requirements around qualification – or Package Performance Qualification (PPQ) – testing. First, PPQ testing now needs to be conducted on frozen and controlled room temperature (CRT) medication – not just refrigerated products as in the past. Second, testing needs to take place at least twice a year compared to only once as previously required.

For ACHC accreditation, shipping and cold chain process requirements are markedly similar to those of URAC. ACHC requires that patients be informed of the expected time frame for delivery and that written policies and procedures (P&Ps) be established and implemented to address the timeliness of shipping, shipping errors, turnaround time, and lost shipments. Additionally:

- Organizations must have P&Ps in place that address proper medication packing to ensure stability; appropriate sanitation, light, and temperature during the course of delivery; alternative methods for medication delivery in case of a disruption in the distribution process; and a periodic validation method to monitor whether containers maintain the specified temperature requirements.

- Pharmacies must also have the proper tools to comply with cold chain packaging requirements, including shipping supplies, shipping diagrams, and proper staff training. Perhaps most crucial is establishing packaging diagrams, which are validated instructions on how to package a cold chain item depending on external temperature. This provides staff with a visual aid to facilitate consistent packaging.

Various vendors provide packaging diagrams that have undergone rigorous testing to assure maintenance of 2˚C to 8˚C in specific external temperature ranges and include validation documents. However, neither URAC nor ACHC requires a pharmacy to utilize an outside vendor to provide these validated documents; pharmacies can develop and validate their own shipping process, if desired.

IV. Testing of Packaging

Several years ago (2014), Zebra technologies asked an independent testing lab to source the five most commonly used packaging technologies used by specialty pharmacies and evaluate their performance against a commonly used testing standard and the packaging manufacturer's own claims. In short, the outcome of this study and the data developed still holds true as many specialty pharmacies continue to purchase and use these same packaging technologies today.

The important points of this study are:

1. "Validated pack-outs" don't always provide the level of insulated protection as claimed (by the packaging manufacturer) and are often not engineered to endure excessive temperature exposure.

2. A Best Practice for pharmacies is to conduct PQ (Performance Qualification) testing specific to their geography and medications, to ensure that packaging is performing as expected – which includes testing under various weather conditions and shipping duration.

3. Visual temperature indicators should still be used to:
    a. Alert patients to medication that has been potentially damaged by exposure to extreme temperatures during the shipment process
    b. Reduce unnecessary medication reshipments due to patients subjectively thinking a medication is "too warm" or "too cold." Without a temperature indicator, it is impossible to know if an unacceptable exposure has occurred.

c. Minimize unnecessary medication waste and uncertainty when shipments are delayed and go beyond anticipated time in transit. Temperature indicators can identify when medications are exposed to extreme temperatures.

The full study can be found at:
https://temptimecorp.com/2019/02/11/the-cold-hard-facts/.

The White Paper is available at:
https://temptimecorp.com/wp-content/uploads/2019/02/white-paper-Thermal-Shipping-Technologies-Cold-Hard-Facts-rev2.pdf.

The following is an article that describes the problem and solution that Walmart pharmacy went through to ensure drug product integrity is maintained when shipping to Hawaii.

Walmart's New Pharma Packaging Survives High Temperatures and Cuts Costs

As powerful as Walmart is, it can't change the weather. That's why James Soucey, director of clinical services for Walmart's Specialty Pharmacy in Lake Mary, FL, had a problem shipping to the state of Hawaii. The state's logistics and warm temperatures were wreaking havoc on the company's mail-order shipments of high-value, temperature-sensitive prescription drugs to patients in Hawaii with special health conditions or complex, chronic conditions. Patients were receiving shipments that were too warm, which denaturized some of the protein-based biological products, and sometimes rendered the medications ineffective.

First problem, common carriers that transport the medications were occasionally holding the Hawaiian shipments at a main hub until there were enough packages to warrant a delivery to outlying islands. This delay was causing shipments to exceed the cold-chain capacity of the packaging.

The second issue was the availability of patients to receive the shipments***. Even though the Specialty Pharmacy staff was diligent in contacting the intended recipients to ensure they would be home when the drugs were set to arrive, sometimes things came up, people weren't home when they said they would be, and consequently, the package containing the medication would, perhaps, sit on a doorstep for hours at a time, often in the hot sun. This would also exceed the packaging's temperature-insulating capabilities.*** "We saw an increasing number of 'reships,' sometimes at a cost of as much as $1,500 for new medications," recalls James Soucey, director of clinical services for Walmart Specialty Pharmacy. "We needed a solution."

Soucey reassessed Walmart Specialty Pharmacy's packaging method for temperature-sensitive pharmaceuticals. This included not only cold-chain products that require maintenance of 2 to 8 deg C, but also products in controlled-room temperatures that require maintenance of 20 to 25 deg C.

One example of the latter group is GLEEVEC®, an oncology drug that can cost roughly $8,000 for one therapy cycle. If GLEEVEC is subjected to extreme heat, the medication capsules can melt together like gummy candy.

First line of defense

Keeping its cool (or warmth, depending on the product) the GreenBox maintains a temperature for days. It's also reusable and recyclable.

Soucey decided that the Greenbox packaging warranted further investigation, so in early 2008, he initiated a validation procedure that involved transporting temperature-monitored test shipments to customers in Hawaii and Alaska. After months of field tests, Walmart Specialty Pharmacy began using the Greenbox 12 for shipments to Alaska and Hawaii. The pharmacy staff utilized TempTales temperature monitors from Sensitech (www.sensitech.com) in each package to measure both ambient and medication temperatures throughout each product's shipment. Currently, Walmart Specialty Pharmacy is using Greenbox packaging for shipments to outlying areas, primarily Alaska and Hawaii. Inflater Packs are being used for specific drugs for all of the U.S.

Of note, TempTales temperature monitors are data loggers used for testing purposes only. They are not disposable nor are they a feasible option for routine shipment of pharmaceuticals.

The full article can be found at:
https://www.packagingdigest.com/packaging-design/walmarts-new-pharma-packaging-surviveshigh-temperatures-and-cuts-costs.

V. Policy Enactment

Currently, there are no states mandating the use of temperature monitoring tags. The state of Georgia however does have the following rule related to mail-order prescriptions:

> **Rule 480-48-.02 Conditions for Use of Delivery by Mail**
>
> (1) Any pharmacy can regularly employ the U.S. Postal Service or a common commercial carrier to deliver a drug which requires a prescription to a patient only after the patient has requested that a pharmacy deliver by mail his/her filled prescription drugs. Any pharmacy providing delivery by mail to its patients is required to follow applicable Georgia laws and rules.
> (2) A mail order pharmacy located outside this state is required to follow all applicable pharmacy and drug rules and laws of the state in which the pharmacy is physically located.
> (3) A mail order pharmacy shall ensure that all prescription medications are delivered to the patient in accordance with standards of the manufacturer, United States Pharmacopeia, Federal Food and Drug

Administration and other recognized standards. ***A pharmacy shall ensure integrity of any drug requiring temperature control other than "room temperature storage" that is delivered by mail order and provide a notification to the patient of the timeliness in addressing the proper storage of the medication.***

(a) ***The shipping method may include the use of temperature tags, time temperature strips, insulated packaging, or a combination of these.***

(b) The notification method may be by verbal, written, electronic, or other technological means. If verbal, then the pharmacy must document the notification and maintain such documentation.

VI. Summary

1. Currently there are no studies assessing potential false-positive and false-negative readings with temperature monitoring tags. Also, most tags provide a snap-shot in time indicating that an excursion occurred but they cannot measure temperature over time. However, visual temperature indicators are feasible and could still be used as an added measure of quality assurance but should not be the primary means for ensuring product integrity.

2. Cold chain distribution requirements defined by URAC and ACHC are important and necessary to ensure drug product integrity throughout transport. Pharmacies that ship pharmaceuticals should conduct package performance qualification tests specific to their geography and medications, to ensure that packaging is performing as expected. Documentation should be retained on-site and available upon inspection.