Process Improvement and Cost Reduction Opportunities by a Change in the Packaging Material of Human Thrombin Component Coming in Vials

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Abstract *— Human Thrombin is a bleeding control agent that is formulated, filled into a glass vial, and lyophilized to maintain stability. In order to be shipped, the vials are packaged in a container made from cardboard material. Particulate matter coming from the packaging is transferred to the vials which results in the addition of a cleaning step prior to subsequent processing. An alternate plastic packaging material consisting of Polyethylene Terephthalate and Polypropylene was evaluated. Assessment of the cleaning process showed that a change in the current packaging represents an improvement in terms of the elimination of a non-value- added step and the associated labor cost. Additional evaluation demonstrates that this change also implies a reduction in scrap and in the costs applied for shipping. By identifying and implementing an alternate packaging material, product quality is improved, and non-value-added process steps and associated costs are eliminated, which will result in costs savings.*

Key Terms — *Cleaning Process, Cost Reduction, Packaging Container, Particle Matter*

INTRODUCTION

Human Thrombin is a protein isolated from human plasma that plays a critical role in coagulation. Thrombin in combination with other hemostatic agents is used in surgical applications to achieve hemostasis. According to Gale [1], "hemostasis is the physiological process that stops bleeding at the site of an injury". Thrombin based sealants are commonly used intra-operatively to promote coagulation and minimize blood loss [2]. Once the agent is applied to the affected area, the blood flow is shielded, clotting is facilitated, and the time to achieve hemostasis is shortened [3].

Human Thrombin comes lyophilized in glass vials from the Manufacturer. Lyophilization is also known as freeze-drying and the result is a solid-state product [4]. This process improves the long-term stability of the protein and also provides for easy handling during shipping and storage [4]. Manufacturing process from Thrombin encompasses several steps that include product formulation, filtration, filling into glass vials, lyophilization, and packaging. The packaging consists of shipping cases and trays made of cardboard. Two Thrombin configurations are manufactured: 5mL and 10 mL. The 5mL configuration allows for 8 trays containing 50 vials each for a total of 400 vials per case. The 10 mL configuration allows for two (2) trays containing 35 vials each for a total of 70 vials per case. The cases are then loaded into pallets for shipping. The 5 mL configuration allows for 24 cases per pallet, while the 10 mL configuration allows for 32 cases per pallet.

At the customer location, each vial is loaded along with other components in a pouch and sealed. These pouches are inspected per product Batch Record and Material Specification requirements for contents, integrity, and cleanliness. Cleanliness requirements are established as a pouch free of visible contaminants including particulate matter.

In order to meet the requirements for cleanliness, upon subsequent receiving and inspection activities, the Thrombin product is released and transported to a designated area where a cleaning process is performed for the removal of particulate matter generated from the cardboard packaging material. This step consists on the unloading of the vials from the packaging components and cleaning. A mechanism for cleaning was designed where the vials are placed in

a stainless-steel bin and a current of air is blown over the vials. The removed particles are collected in a filter placed below the stainless-steel bin. Upon subsequent cleaning, the vials are placed into plastics bins, labeled, and delivered to the manufacturing cleanroom for processing. Figures 1, 2, 3, and 4 depict the cleaning process as follows:

Figure 1
Particulate Matter coming from the Cardboard Packaging Material

Figure 2
Placement of Filter for Particle Collection

Figure 3
Unloading of Vials into Stainless-steel Bin

Figure 4
Cleaning of Vials using Blown Air

Alternatives are available to substitute the cardboard from the packaging of the Thrombin vials. These alternatives include the use of plastic material. Plastic use accounts for around 30% of the total materials used in the packaging industry due to its performance [5]. Common plastic packaging includes thermoplastics, such as Polyethylene (PE), polyvinylchloride (PVC), polypropylene (PP), polyester (PET), polystyrene (PS), polycarbonate (PC), and others [5]. Guo, et al, [5] mentions that packing is a major source of recycled plastics. Methods for recycling include separation, pretreatment, melting, granulation, molding amongst others [5]. According to Guo, et al, [5], polyethylene terephthalate (PET) is widely used in the packaging industry and has a large number of consumption and high recovery value. On the other hand, PP holds properties such as excellent processability and chemical resistance [6]. Furthermore, Aumnate, et al, [6] states that due to its physical properties such as high strength and rigidity, PP is widely used as packaging material. In addition, to its physical properties, plastic owns other characteristic such as ease of manufacturing and low cost [6]. These characteristics make plastic suitable for the packaging of Thrombin and proposes an alternative for particle matter reduction coming from cardboard material.

This project aims to establish an alternate packaging for Thrombin vials that results in the elimination of particle matter from the cardboard current packaging. The project also seeks the elimination of the cleaning process by changing the

packaging material and to evaluate the associated cost reduction. Cost saving related to reduction of pallets used for shipping will also be assessed.

EXPERIMENTAL

Alternate packaging materials and configuration was assessed along with the Supplier of Human Thrombin. The selected alternative includes two types of plastic material; vial trays made of Polyethylene Terephthalate (PET) and shipper case made of Polypropylene (PP). The proposed prototype was evaluated, and several considerations were made including fitness for use for Thrombin packaging and transportation, fitness for use in the manufacturing operation, cost, and recycling viability. Figure 5 shows the new plastic packaging prototype.

Figure 5
New Plastic Packaging Prototype

Determination of Cost Savings Opportunities

The cleaning of the Thrombin vials was evaluated to determine the labor hours applied to the process, the associated cost, along with opportunities for waste reduction. The process was evaluated starting from the cleaning area setup, unpacking of the vials from the shipper case and trays, cleaning, placement into plastic bins, and labeling, up to the disposal of the packaging material. An operator is designated to perform the cleaning on a determined quantity of vials based on production schedule. The labor hours applied were determined for each code; 5 mL and 10 mL. The manufacturing schedule was used to obtain the quantities of vials needed in production on a monthly basis considering both codes. The labor hours applied were multiplied by the labor cost to determine the total cost per month. The results were added to obtain the yearly cost for cleaning. Subsequent assessment was made on scrap data related to Thrombin pouches rejections at the Area for Final Processing due to Particle Matter to determine the associated scrap reduction.

On the other hand, the new packaging provides for a new configuration that allows more vials per case. For 5mL Thrombin code, new packaging configuration allows for 8 trays containing 70 vials each for a total of 560 vials per case. For 10 mL Thrombin code, new packaging configuration allows for 6 trays containing 30 vials each for a total of 180 vials per case. Thus, cost savings opportunities were explored from a reduction of the number of pallets used for shipping. As the number of vials per case is increased in the new packaging, a reduction in the number of boxes is represented, which translates to a reduction in the number of pallets. Information was available by the Planning Department on the ordered quantities of vials from January to June 2021 for each code. The approximated number of boxes needed was obtained by dividing the ordered quantity of vials by the quantity of vials that fit per case. Comparison was made between the number of boxes for the current packaging and the number of boxes for the new packaging. These numbers were used to calculate the number of pallets and the potential cost saving coming from a reduction.

RESULTS AND DISCUSSION

The selection of the new packaging was based on the current use of similar packaging materials and configurations by the supplier and associated feasibility studies. Packaging process and conditions at the supplier facility were evaluated to assure proper controls are in place as to avoid the introduction of new particles to the vials. The new packaging was evaluated at the customer site involving all impacted areas for fitness for use, recycling capability, and ergonomics. The assessment determined the viability of new packaging for use.

Cleaning Process Evaluation

The cleaning step for Thrombin vials occurs prior to the delivery of the raw material to the cleanroom for processing and is associated to the Thrombin pouching process. Upon assessment of the process flow, it is determined that the cleaning step creates material flow interruptions and waste in the form of transportation. This type of waste is created with the movement of vials from the storage to the cleaning location, and with the transferring of vials from the original packaging container, to the stainless-steel bin for cleaning and, subsequently, to a new plastic container. Figure 6 shows the Process Flow for Cleaning.

Figure 6
Cleaning Step Process Flow

The Cleaning step has an associated time and cost as presented in Table 1.

Table 1
Time and Labor Cost Applie to Thrombin Vials Cleaning Step

Thrombin Code	Evaluated Quantity (ea)	Average Time for Cleaning (hr)	Labor Cost Applied per Hour
5 mL	2,400	0.67	39.94
10 mL	5,200	4	39.94

The time associated for the cleaning of a standard quantity of 2,400 and 5,200 vials for 5mL and 10 mL codes, respectively, was evaluated. The time and labor cost applied will depend upon the requested quantity for cleaning following the Manufacturing Schedule. An evaluation of the labor hours applied, and total cost incurred was performed from January 2020 up to Mid-April 2021, as presented in Table 2.

Table 2
Thrombin Vials Cleaning Step Applied Time and Labor Cost

Month-Year	Thrombin Size	Quantity Cleaned	Labor Hours Applied	Total Cost $
Jan-20	5mL	34,052	9.46	377.79
Jan-20	10mL	31,180	23.98	957.95
Feb-20	5mL	10,368	2.88	115.03
Feb-20	10mL	41,220	31.71	1,266.41
Mar-20	5mL	23,379	6.49	259.38
Mar-20	10mL	30,000	23.08	921.69
Apr-20	5mL	24,260	6.74	269.15
Apr-20	10mL	57,200	44.00	1,757.36
May-20	5mL	18,195	5.05	201.86
May-20	10mL	10,400	8.00	319.52
Jun-20	5mL	12,130	3.37	134.58
Jun-20	10mL	50,000	38.46	1,536.15
Jul-20	5mL	40,768	11.32	452.30
Jul -20	10mL	52,000	40.00	1,597.60
Aug-20	5mL	45,655	12.68	506.52
Aug-20	10mL	46,800	36.00	1,437.84
Sep-20	5mL	29,154	8.10	323.45
Sep-20	10mL	49,950	38.42	1,534.62
Oct-20	5mL	34,560	9.60	383.42
Oct-20	10mL	33,524	25.79	1,029.96
Nov-20	5mL	12,300	3.42	136.46
Nov-20	10mL	34,048	26.19	1,046.06
Dec-20	5mL	29,952	8.32	332.30
Dec-20	10mL	52,480	40.37	1,612.35
Jan-21	5mL	30,848	8.61	343.95
Jan-21	10mL	46,976	36.14	1,443.25
Feb-21	5mL	38,016	10.61	423.88
Feb-21	10mL	65,408	50.31	2,009.54
Mar-21	5mL	49,536	13.83	552.32
Mar-21	10mL	40,064	30.82	1,230.89
Apr-21	5mL	6,912	1.93	77.07
Apr-21	10mL	30,848	23.73	947.75

The cleaning step represents a non-value-added activity and its elimination proposes the removal of the cost associated which, from January 2020 up to Mid-April 2021, is calculated as $25,538.37.

Particulate Matter Reduction

The cleaning step is implemented as a control measure to mitigate the incidence of cardboard

Particle Matter in the Thrombin pouch component. However, no assessment is in place to demonstrate its effectiveness. High incidences of rejected pouches at the Area for Final Processing are observed due to Particle Matter. Evaluation on the scrap for rejected units was performed from January to Mid-April 2021. Rejected samples include particles from cardboard coming from the packaging material.

For the 10mL Thrombin Pouch Codes, Particle Matter accounts for 79% of the scrap associated to Final Processing, as presented in Figure 7. In the same manner, Particle Matter accounts for 95% of the scrap associated to the Final Processing of the 5mL Thrombin Pouch Code, as presented in Figure 8.

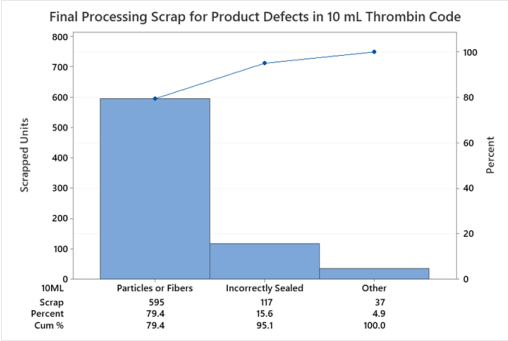

Figure 7

Top Category Defects for Final Processing Area Scrap in 10 mL Thrombin Code

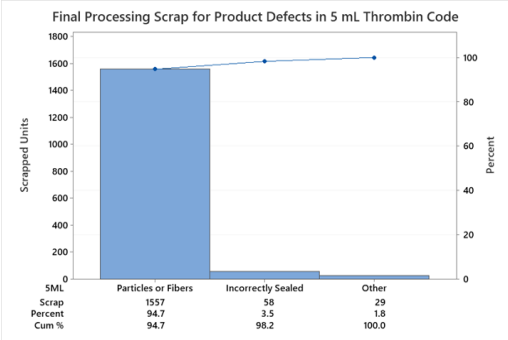

Figure 8

Top Category Defects for Final Processing Area Scrap in 5 mL Thrombin Code

Classification of particles demonstrates that cardboard accounts for an average of 11% of the particles found on rejected pouches for 10 mL codes and for a 4.0% on 5mL codes as depicted in Figures 9, 10, 11, and 12.

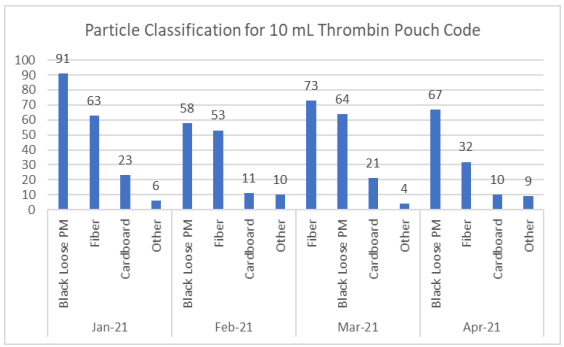

Figure 9

Particle Matter Classifications and Quantities for 10 mL Code

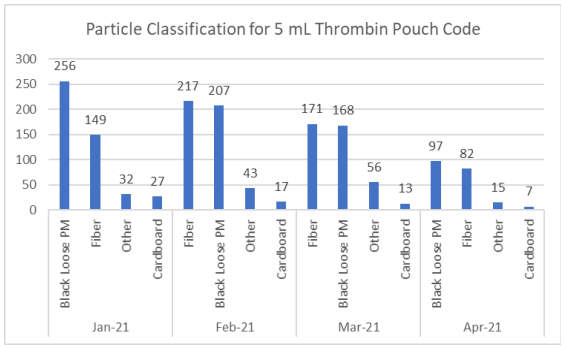

Figure 10

Particle Matter Classifications and Quantities for 5 mL Code

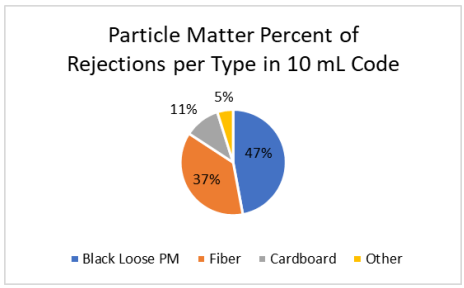

Figure 11

Percent of rejections for cardboard particle matter in 10 mL Code

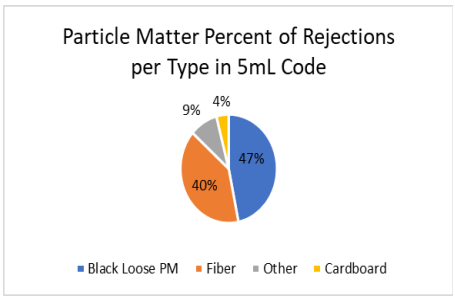

Figure 12

Percent of rejections for cardboard particle matter in 5 mL Code

It is expected that this project results in a reduction in the percent of rejections for Thrombin Pouches due to carboard Particulate Matter along with the associated cost reduction in scrap. An evaluation with the available cost data from January to Mid -April 2021 was made and a reduction in the total scrap cost for particulate matter can be estimated as shown in Figure 13.

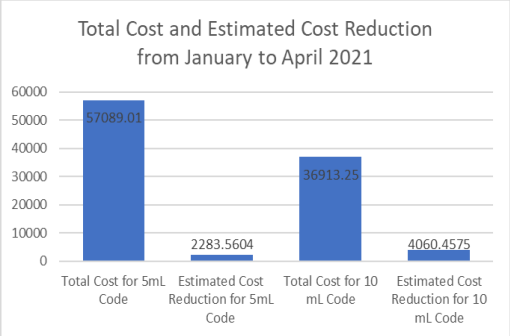

Figure 13

Total Cost and Estimated Cost Reduction in Scrap for Particulate Matter resulting from the elimination of Carboard Particles

Cost Savings Coming from Pallet Reduction

The new packaging provides for a new configuration that allows more vials per case as presented in Table 3.

Table 3

Vials and Pallet Quantity Comparison between Current and New Packaging Configurations

Code	Current Qty of Vials per Box	New Qty of Vials per Box	Current Qty of Pallets	New Qty of Pallets
5mL	400	560	24	24
10mL	70	180	32	24

Cost reduction was evaluated using the actual and forecasted quantities from January to June 2021. With the volume of pallets being the determining factor in the cost for shipping, this reduction is demonstrated as depicted in Table 4 and 5. Comparison between the current and estimated cost was performed as presented in Figure 14 and 15.

Table 4

Box and Pallet Quantity Comparison between Current and New Packaging Configuration and Estimated Price Difference for 5mL Code

Month	Qty of Ordered Vials	Current Qty of Boxes	Estimated Qty of Boxes	Current Qty of Pallets	Estimated Qty of Pallets	Pallet Cost $	Cost Difference $
Jan	60,759	152	108	6	5		2,583.45
Feb	66,936	167	120	7	5		2,846.09
Mar	66,482	166	119	7	5	$1,428.66	2,826.79
Apr	44,383	111	79	5	3		1,887.15
May	49,339	123	88	5	4		2,097.88
Jun	62,170	155	111	6	5		2,643.45

Table 5

Box and Pallet Quantity Comparison between Current and New Packaging Configuration and Estimated Price Difference for 10mL Code.

Month	Qty of Ordered Vials	Current Qty of Boxes	Estimated Qty of Boxes	Current Qty of Pallets	Estimated Qty of Pallets	Pallet Cost $	Cost Difference $
Jan	65,788	940	365	29	15		20,202.59
Feb	30,193	431	168	13	7		9,271.86
Mar	49,844	712	277	22	12		15,306.41
Apr	48,045	686	267	21	11	1,428.66	14,753.96
May	46,704	667	259	21	11		14,342.16
Jun	51,135	731	284	23	12		15,702.86

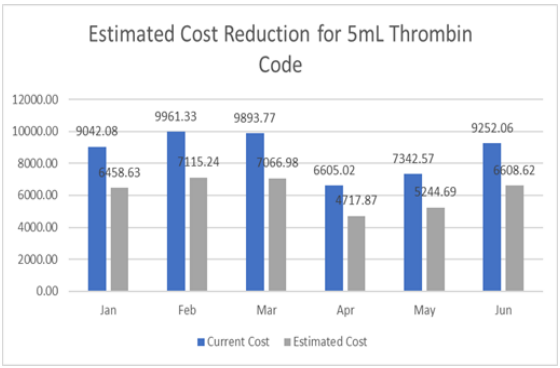

Figure 14

Pallet Cost Reduction Evaluation using Actual and Forecasted Quantities of vials from January to June 2021 for 5mL Thrombin Code

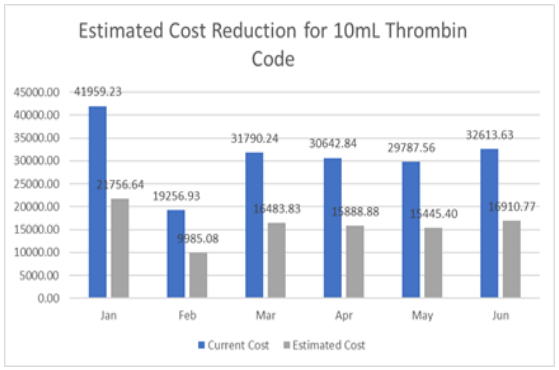

Figure 15

Pallet Cost Reduction Evaluation using Actual and Forecasted Quantities of vials from January to June 2021 for 10mL Thrombin Code

Based on the available data on the ordered quantities of vials from January to June 2021, it is determined that the new configuration proposes a cost reduction in shipping activities resulting from the higher quantity of vials that fit per box and the associated decrease in the number of boxes and pallets. Taking into consideration the average current cost and the average cost difference, this reduction is calculated as approximately 29 % for 5 mL codes and 48% for 10 mL codes.

CONCLUSIONS

Assessment of the Thrombin vials cleaning shows that a change in the current packaging from cardboard to a new plastic configuration represents an improvement in terms of the elimination of a non-value added step, along with the elimination of the labor cost applied for the process. Additional evaluation on scrap data for Thrombin pouches rejected due to particulate matter, demonstrates that this change also implies a reduction in the percent of scrap and an associated cost reduction coming from a decrease of cardboard particles. Classification of particles demonstrates that cardboard accounts for an average of 11% of the particles found on rejected pouches for 10 mL codes and for a 4.0% in 5mL Thrombin Pouches Codes.

It is also demonstrated that the new plastic configuration results in a reduction in the costs applied for shipping. This reduction comes from a decrease in the number of pallets, being the volume of this shipping component the determining factor for cost. The available data on the orders of vials from January to June 2021, allowed to demonstrate a cost reduction of approximately 29 % for 5 mL codes and 48% for 10 mL codes.

This study is aligned with the Company initiative for Cost reduction. By identifying and implementing an alternate packaging material for the Thrombin vials, product quality will be improved and non-value-added process steps and associated costs are eliminated, which results in costs savings. This study also promotes further areas of research including reduction of defects introduced by the handling of vials during the cleaning process, such as cracks.

REFERENCES

[1] A.J. Gale, “Current Understanding of Hemostasis”, Toxicologic Pathology, vol. 39, no. 1, 2011. [Online serial]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3126677/. [Accessed Mar 29, 2021].

[2] E. Echave, I. Oyagüez, and M.A. Casado, “Use of Floseal®, a human gelatine-thrombin matrix sealant, in surgery: a systematic review”, BMC Surgery, vol.14, no.111, 2014. [Online serial]. Available: https://bmcsurg.biomedcentral.com/articles/10.1186/1471-2482-14-111. [Accessed Mar 29, 2021].

[3] D. Kamamoto, T. Kanazawa, E. Ishihara, K. Yanagisawa, H. Tomita, R. Ueda, M. Jinzaki, K. Yoshida, M. Toda, “Efficacy of a topical gelatin-thrombin hemostatic matrix, FLOSEAL®, in intracranial tumor resection”, Surgical Neurology International, vol. 11, no. 16, 2020. [Online serial]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7049874/. [Accessed Mar 29, 2021].

[4] J.C. Kasper, W. Friess, “The freezing step in lyophilization: Physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals”, European Journal of Pharmaceuticals and Biopharmaceutics, vol. 78, no. 2, 2011. [Online serial]. Available: https://www.sciencedirect.com/science/article/pii/S0939641111001111. [Accessed Mar 29, 2021].

[5] J.C. Guo, X. Li, Y. Guo, J. Ruan, Q. Qiao, J. Zhang, Y. Bi, F. Li “Research on Flotation Technique of separating PET from plastic packaging wastes”, Procedia Environmental Sciences, vol. 31, 2016. [Online serial]. Available: https://www.sciencedirect.com/science/article/pii/S1878029616000256. [Accessed Apr 09, 2021].

[6] C. Aumnate, N. Rudolph, M. Sarmadi, “Recycling of Polypropylene/Polyethylene Blends: Effect of Chain Structure on the Crystallization Behaviors”, Polymers, vol. 11, no. 9, 2019. [Online serial]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6780393/. [Accessed Apr 09, 2021].