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Scientific poster prepared for ISPOR 2023 Boston

Assessing the Risks and Benefits Associated with Automation during Cell Expansion Processes at Cell and Gene Therapy Manufacturers

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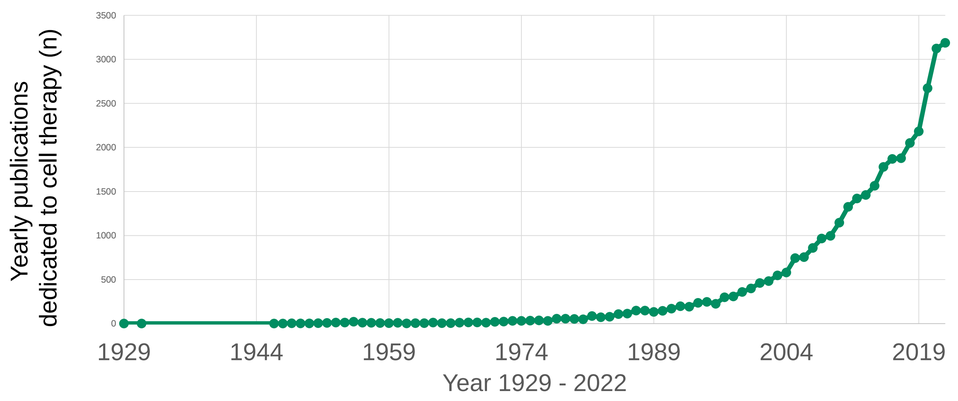
Introduction

- Cell and gene therapy (CGT) was first mentioned in a scientific publication in 1929. By 2022, its footprint had grown to 3188 dedicated publications per year (see Figure 1).
- This rapidly growing field of therapy aims to use cells to treat various illnesses and conditions. In the past 15 years, there have been significant advancements in this field, particularly in the areas of stem cell therapy and CAR-T cell therapy. Stem cell therapy involves the use of specialized cells that can differentiate into various types of tissues to repair damaged or diseased tissue. Researchers have made significant progress in the development of induced pluripotent stem cells, which are adult cells that have been reprogrammed to behave like embryonic stem cells. These cells have the potential to be used to treat a variety of diseases, including heart disease, diabetes, and Parkinson's disease. CAR-T cell therapy involves taking a patient's own immune cells, called T cells, and modifying them to recognize and attack cancer cells.[2-6]
- As CGT is expanding its footprint and developing life-changing therapies, companies are seeking out cost-efficient opportunities, standardization, and scalability.[4-6]
- CGT manufacturing can be split into multiple components, including the cell expansion (CEP) process[7] and the fill and finish (F&F) process.[8] If insufficiently performed, both can compromise product quality and efficacy.[7-8] Coupled with the high cost of CGT products, the criticality of F&F and CEP requires examination.[9]

Figure 1: Evolution of Cell Therapy Scientific Publications



Objectives

- The objective of our research was to assess the costs and benefits of manual cell handling versus automated cell expansion (CEP) and fill and finish (F&F) procedures.

Methodology

- Our methodology was constructed based on two steps: an in-lab experiment and a quantitative and qualitative survey among cell and gene manufacturers.
- First, the in-lab experiment was created to run a real-life comparison of risks presented by F&F to the cell product. Two modalities for F&F procedures were compared: manual F&F versus automated F&F (not user- or operator-dependent). For each risk identified, an estimation model was created to define the likelihood of the event occurring per 1000 units produced. This was combined with the economic value from a cost of goods perspective and the costs per unit produced for both modalities.
- Second, during quantitative interviews and an Adelphi panel approach with 47 participants active in the CGT manufacturing process at different manufacturers, respondents were prompted for their risk experience during the manual CEP and how they perceived automation could alter their experience.

Results

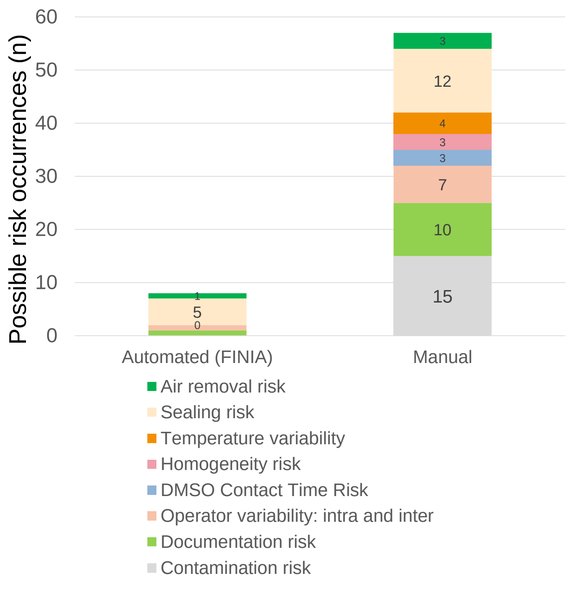
Risks Associated With the Fill and Finish Procedure

- In our paradigm, during the F&F procedure, 9 different risks were identified: contamination risk, documentation risk, operator variability, dimethyl sulfoxide (DSMO) contact time risk, homogeneity risk, temperature variability risk, sealing risk, and air removal risk.
- For manual processes, 57 moments of risk were identified; for automated procedures, 8 moments. Within the area of manual cell handling, the 3 most common risks included contamination risk (26%), sealing risk (21%), and documentation risk (18%), which may result in a loss of cell product or a delay in delivery of the cell product to the patient (see Table 1 and Figure 2)

Table 1: Risk Comparison, Automated vs. Manual F&F

Type of Risk	Number of Occurrences	
	Automated F&F	Manual F&F
Contamination risk	0	15
Sealing risk	5	12
Documentation risk	1	10
Variability: intra-operator and inter-operator	1	7
Temperature variability	0	4
DMSO contact time risk	0	3
Homogeneity risk	0	3
Air removal risk	1	3
Total	8	57

Figure 2: Risk Comparison, Automated vs. Manual F&F



Results

- The degree of risk of loss of a cell product or a delay of its delivery to the patient was not considered equal for the different risk types. Contamination risk and sealing risk were assessed by the experts as being most likely to cause loss of the cell product (see Table 2).

Table 2: Likelihood of Losing the Cell Product as a Function of Risk

Risk Type	Risk Assessment	Likelihood of Losing Cell Product
Contamination risk	Very high	85% to 100%
Sealing risk	High	85%
DMSO contact time risk	Low to moderate	30%
Homogeneity risk	Low to moderate	30%
Temperature variability	Low to moderate	30%
Air removal risk	Low to moderate	30%
Documentation risk	Low	15%
Inter-operator and intra-operator variability	Very Low	< 1%

Cost of Risks During the Fill and Finish Procedure

- We combined the likelihood of risk events during F&F with the cost of a cell product estimated at USD $470 000 per product;[10] assuming a yearly production of 1000 cell therapy units, our research determined that the value of cell product lost for automated F&F was USD $0.98 million per yea, whereas the total financial value of cell products lost for manual F&F was USD $5.34 million per year.
- These savings related to loss of cell product need to be adjusted for the cost of the F&F procedure itself. For manual F&F, the yearly cost for 1000 units was an estimated USD $0.75 million; however, for automated F&F, it was USD $1.21 million. To estimate the total F&F procedure cost, the following parameters were considered: facility cost (e.g., clean room), personnel, operator hands-on time, operator training, equipment, biosafety cabinet, disposables, welder, sealer, cryoprotectant (100 mL), and buffer.
- Combining the cost of risks with the cost of production return a yearly saving of USD $3.99 million for automated F&F (Finia® Fill and Finish System, Terumo Blood and Cell Technologies) compared to manual F&F (See Table 3).

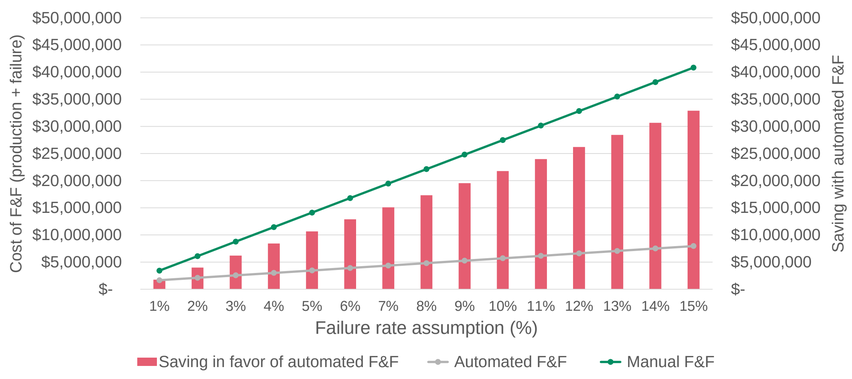
Table 3: Cost Comparison, Fill and Finish

	Automated F&F	Manual F&F
Cost of Manufacturing (USD)	1,209,962	751,700
Cost of Risks (USD)	898,771	5,343,157
Total (USD)	2,108,734	6,094,858
	Savings with automated F&F (USD)	3,986,124

Sensitivity Testing

- The cell expansion process is believed to be one of the leading drivers of cell manufacturing failure.[11] In the calculation above (See Table 3), a 2% cell manufacturing failure rate was assumed. However, there may be a large range of failure rates. During a targeted literature review, failure rates ranging from 3% to 18% were identified.[11-14] Some publications even suggest a difference between failure rates in manual (10%) versus automated processes (3%).[12] Hence our 2% cell manufacturing failure rate was a conservative assumption regarding parity between automated and manual cell manufacturing, and therefore realized savings may be greater (see Table 2).

Figure 3: Cost Comparison, F&F Methods as a Function of Failure Rate



Risks related to the cell expansion process

- The most frequent CEP-related risks that occurred, ranked in order of severity, included (n: number of experts identifying this risk) risk to process reproducibility (n = 16), inconsistency in the final product (n = 14), additional man hours required (n = 14), low viability (n = 7), contamination issues (n = 5), and risk to disposable set stability and integrity (n =3).
- The main drivers identified by the experts to automate the CEP included having a functionally closed system (91%), reducing product variability (84%), complying with Good Manufacturing Practices (GMP) for scaling up (84%), reducing human error (84%). From a cost perspective the following drivers of CEP were identified: labor (28%), facilities (25%), consumables (16%), batch contamination (13%), labor training (10%), and quality control and traceability (8%).
- According to expert opinion, automation of the CEP may result in 62% reduction of operator time and 58% reduction of labor force cost.

Conclusions

- CGT manufacturers may benefit from automating both the fill and finish and cell expansion processes to achieve the lower anticipated risks and costs that occur when switching from manual cell handling to automation. Moreover, this reduction is associated with a financial savings.

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