Does Rewarding Quality Improve Behavior in Pharmaceutical Production? A Serious Gaming Approach

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Abstract

Purpose: Counterfeit, adulterated, and misbranded medicine (CAMM) are a threat to the pharmaceutical supply chain (PSC). In an effort to safeguard patients pharmacy-level testing is emerging. However, these on-the-ground (OTG) facilities such as the University of Kentucky Central Pharmacy often work with limited equipment and staffing resources. Limitations such as these make it infeasible to scan every single drug passing through. To counter this, risk models are used to inform personnel of drugs that may be low-quality. However, these models are not creative or imaginative like the humans behind intentionally counferit, adulterated or misbranded medicine. Hence, leaving investigators one step behind. It has been suggested that rewarding quality may improve human behavior in this realm. However, with current methods testing this hypothesis would be impractical in terms of cost and time. In this paper a novel serious gaming approach is developed such that human creativity and imagination can be captured in a virtual environment. Putting the game system in action the hypothesis that quality will improve human behavior as it relates to the PSC is tested.

Methods: A novel serious gaming system is used to capture human action in a virtual pharmaceutical manufacturing environment. Utilizing the commercial game BigPharma in combination with Python 3 shell additions N=4 players play through a series of 3 games with varying objectives. The first players are profit motivated. In the second game players are quality motivated through earning quality points through completion of quality attributed tasks. Lastly, the third game players are encouraged to maximize profit and quality. Decision-making is captured through script outputs and screen-recordings. Monitoring this data players' in-game revenues, unethical techniques and frequency of unethical behavior are compared between games.

Results: Data suggests that rewarding quality may improve players' ethical decision-making. Indeed, all players were 100% ethical in worker-level decisions when solely rewarded for quality-gaining an average shell score (SS) of 7 (perfectly ethical). Compared to an average SS of 5.75 recorded in profit-motivated play. After reintroducing profit in game 3, worker fraud re-emerged but at a much lower frequency than present in game 1 (where quality rewards were absent)—yielding an overall SS of 6.75 in game 3. Ethical scores (ES) were used to reflect players' management strategies and were seen to improve moving from game 1 to 2. However, ES were consistent across the board, moving from game 2 to game 3 results. Suggesting that after introducing quality rewards, profit did not corrupt or improve players' ethical decision-making.

Conclusion: This study has acted as a feasibility study for capturing and studying unethical decision-making as it relates to the PSC. Behavior observed in-game aligned well with behavioral and crime theories such as the Fraud Triangle theory. Further variables such as large profitability were identified to improve current risk models used by pharmacy-level investigators (PLIs). Additionally, data suggests that rewarding quality may improve human decision-making and provides a means for time and cost effective investigations of future suggestions towards safeguarding the PSC.

Keywords: serious gaming, game simulations, counterfeit drugs, substandard medicine, pharmacy-level investigators.

Introduction

The Moreno's 1-year-old son faced a serious *Burkholderia cepacia (BC)* infection. Classified as an objectionable microorganism (Kundrat, 2016) the infection temporarily removed him from the transplant list. Recovering from the infection, he ultimately received his vascular transplant only to have the BC infection return. This time the consequences were severe, leaving him dependent on a ventilator ever since (Lupkin, 2019b). The source of the infection? Docusate sodium, an over-the-counter (OTC) stool softener produced by PharmaTech LLC, a Florida-based company routinely classified as Voluntary Action Indicated (VAI) or Official Action Indicated (OAI) by FDA investigators (Huntington et al., 2016; Mccabe, 2012). Classifications indicating the company's consistent in-compliance with FDA guidelines. This time PharmaTech's neglect to develop cleaning validation procedures for the reverse osmosis purified water system was to blame (Lalama et al., 2016). Lack of cleaning and testing allowed BC growth in the water used to formulate the company's liquid OTC stool softener. The contaminated drug went on to make many sick and allegedly caused the death of at least one infant (*Civil Action No. 17-921*, 2020). Unfortunately, the Monero's are not alone in their story.
The delicate nature of pharmaceuticals means even one CAMM can be disastrous. Indeed, doctors have warned that an estimated 250,000 children a year could die due to counterfeits alone (Sample, 2019). Further, the COVID-19 pandemic has provided ample opportunity for fakes in the forms of vaccines and remedies (Surtees, 2020). Admittedly, Pfizer, one of the largest COVID-19 vaccine producers, has confirmed detecting fake vaccines in Mexico and Poland, where individuals paid up to $1000 for the fraudulent shot (Hopkins and Córdoba, 2021), a highly profitable scheme given that individuals typically receive the vaccine free of charge (DW, 2021). However, this is a foreseeable scheme given estimates predict a $1000 investment in counterfeit prescription drugs can result in a $30,000 return. A 10-fold profit compared to trafficking heroin (Blackstone et al., 2014), making CAMMs an obvious method of choice for criminals. In addition to CAMMs, profitability, it is also less risky compared to violent crimes.

Criminal penalties for CAMM-related offenses are often far less significant than selling illegal narcotics (Blackstone et al., 2014). The penalty can be even less threatening if the CAMM is sourced through a legitimate company. Though acts such as the Prescription Drug Marketing Act of 1987 and False Claims Act are in place to discourage the retail sale of CAMMs, the offense is still common (FDA, 2018d). Companies often settle these claims through cash payouts (Girard, 2009). With settlements ranging from a few thousand to billions of dollars. A list of companies, their offense, and penalty amounts can be explored at https://violationtracker.goodjobsfirst.org/industry/pharmaceuticals.

For more detailed stories of CAMM offenses, we can look to one of the New York Times' 100 notable books of 2019- Bottle of Lies by Katherine Eban (New York Times, 2019). In this book Eban accounts whistleblowers and FDA agents' true stories of management corruption, criminal schemes, and data concealment in generic pharmaceutical companies (Eban, 2019b, 2019a). On a similar note, Roger Bate's book Phake: The Deadly World of Falsified and Substandard Medicines investigates CAMM around the world while also speaking to the difficulties in identifying and eliminating CAMMs universally (Bates, 2012). Indeed, both Eban and Bates detail real stories of how unethical human activities threaten the PSC and distribute CAMMs.

Unethical human decision-making is often at the heart of many CAMM cases. After all, distribution of CAMM provide high-profit incentives, and penalties are often negligible. Further, the probability of overall detection is low given the complex nature of pharmaceuticals and the supply chain (Koh et al., 2003). Indeed, it often requires specialized equipment to identify CAMMs (Campbell and Lodder, 2021b). Making matters worse, regulators charged with safeguarding the PSC have also encountered setbacks since COVID-19 due largely in part to travel bans, leaving a major backlog of inspections and providing more vulnerabilities to the already delicate PSC. In an attempt to catch up, regulators such as the FDA have turned to virtual methods for most document-based inspections (Jeremy Kahn, 2021). However, the vulnerabilities of this technique were soon to be exposed. Just 21 days after the FDA launched their virtual evaluation guidance to industry, whistleblowers alerted the FDA of Eli-Lilly's upper management, altering quality documents (Higgins-Dunn, 2021). Beyond these concerns, the FDA is often facing shrinking resources for inspections while concurrently facing increasing demands posed by new drug products (Campbell and Lodder, 2021b). To further add to the issue, the PSC is often facing shortages, with the COVID-19 pandemic only exacerbating the problem (Bookwalter, 2021; Lee Ventola, 2011). The presence of drug shortages beyond its obvious concerns often leads regulators into more unforeseen issues such as a regulator's dilemma, a phenomenon best described by an example. Imagine a manufacturer is the sole producer of a drug (termed sole-sourced) -a scenario often resulting in unethically high-priced drugs (Alpern et al., 2020; Kolchinsky, 2017). Testing is done, and the FDA finds the manufacturer is selling the drug sub-potently at 80% of the API listed on the label. The FDA is then stuck with a dilemma: allow the manufacturer to continue sales while stating the issue needs to be fixed immediately or force a recall or cease sales of the substandard drug, then causing a drug shortage. A shortage risks patients not receiving their needed medicine at all. Though this is a simplified regulator's dilemma (see(Schilsky, 2018)) it is evident that neither option is optimal for the regulator and leaves them in a compromised position. Meaning, manufacturers often have the upper hand. With that said, most manufacturers handle the responsibility of producing high-quality drugs well. The concern is with those that do not (Campbell and Lodder, 2021a). So, while manufacturers and regulators play cat-and-mouse-like games, and the PSC continues to face significant challenges, where does this leave the patients? An alternative method for safeguarding the PSC is needed, and it is the author's opinion that the solution may lie in pharmacy-level investigators (PLIs).

PLIs may solve patient safety concerns in the PSC by significantly reducing the chance that CAMMs reach patients. Moreover, this method has seen remarkable success as

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demonstrated by Valisure, an online pharmacy that tests each batch of drug before dispensing them to their customers. Since Valisure's inception in 2015, the team has rejected approximately 10% of the drugs tested (Valisure, 2021a). A daunting number given the Center for Disease Control and Prevention (CDC) has previously estimated that only about 1% of America's PSC is counterfeit, adulterated, or misbranded (CDC, 2017). Further, some of the highest-profile recalls and alerts of the past five years can be attributed to Valisure's efforts, including Valsartan, Ranitidine, and Metformin (Valisure, 2021b, 2021c, 2019b). Additionally, Valisure has recently reported benzene in both hand sanitizer and sunscreens (Valisure, 2021d, 2021e). Valisure's work is nothing short of impressive; however, they are currently limited in the delivery forms they test (notably excluding injectables from their work).

Injectable drugs are often considered high risk for instabilities and other quality degrading traits (Galante et al., 1992, 1990). Hence there is a clear need for an injectable-focused PLI. Fortunately, the UK Drug Quality Study (DQS) has stepped in to fill this gap. Launched in 2020, the DQS works to screen injectable drug batches administered at the UK hospital. In doing so, the study aims

1. to test UK Healthcare's incoming drugs for identity and quality to improve patient outcomes,
2. to report adulterated/misbranded drugs to FDA and the public, and lastly,
3. to provide advantageous information for UK Healthcare, such as impending shortages.

Within the short time the study has been active several drugs have been pulled for further investigation. The most notable example was Acetazolamide, which was found to possess around 80-87% of the API labeled amount and resulted in a request for recall (Blankenship, 2021; Fiore, 2021). Additionally, the team has begun to provide rapid communications of their findings. The most recent at the time of this writing-communicating a possible process control issue with the COVID-19 drug, Remdesivir (Almeter et al., 2021). Though the DQS team has been effective, teams like the DQS are always working with limited equipment, time, and staffing resources. Scanning every vial immediately before use is not feasible, and drugs must be prioritized for analysis. A risk scoring system coupled with batch sampling techniques is currently used in the DQS. However, a risk scoring system only allows the team to know about the risks to the PSC are today. It does not predict what the risks will be in the future. Likewise for statistical prediction models which can only come up with what they have been trained on. To begin bridging this gap in predictive modeling capabilities, the authors assert that such models must incorporate the human element (imagination, creativity, etc.). As a sister project to the DQS, the Drug Quality Game (DQG), seeks to move towards enabling humans and all of their unpredictability to be inserted into a virtual PSC environment to be studied. As such, a serious game could discover new or future methods of cheating the PSC enabling regulators and PLI's to be one step ahead.

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As a first step towards the DQG project vision, the current study intends to show that a useful game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing setting can be designed and deployed. To achieve this goal, two distinct sets of tasks were identified. First tasks to achieve the design and deployment of the game system itself. Followed by a set of testable hypotheses to provide proof of the game system's "usefulness".

Design and Deployment: To design and deploy a game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing setting the following goals were identified 1) design a game system able to capture human strategies in a pharmaceutical manufacturing setting, 2) design a game system capable of fidelity in such a setting and lastly, 3) determine the ethical boundaries within the game.

Utility: To provide proof for the value of a game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing setting the following hypotheses are tested (1) a game system is capable of identifying the necessary rewards and penalties to ensure GMP compliance. (2) there are variables in the game that are predictive of real-life human-induced risks to the PSC, and (3) the game can capture unethical techniques which bad actors can use to produce counterfeit, adulterated, and misbranded drugs.

The design and deployment stage of this study is described in sections Game System Design and Defining ethical boundaries-What is considered cheating? This is followed by the Experimental setup and Data Collection, Metrics, and Prompts sections. Results are then provided before concluding.

Game System Design

To successfully design and deploy a game system able to simulate real-life humans and their actions in a pharmaceutical setting, we first designed a game system able to capture human strategies in a virtual pharmaceutical manufacturing setting in addition to designing a game system capable of fidelity in such a setting. Though the later objective is somewhat ambiguous, it is argued that fidelity would exist if the replicated system's fundamental components were present. When considering how to replicate a pharmaceutical manufacturing setting properly, a generic pharmaceutical manufacturing business (PMB) was seen to possess at least three core elements- research (or quality lab), processing, and marketing/business. After identifying these elements, the commercial off-the-shelf (COTS) strategy game, BigPharma (developed by Twice Circle) was then selected for the basis of the virtual PMB. Additionally, BigPharma allows for modification, a feature used to improve fidelity in several ways, including implementing realistic drug names and altering loading screen texts (See Appendices 1 and 2 for modification details).

Together the BigPharma's primary design and investigators' modifications were deemed to possess a sufficient level of fidelity for the study's purposes. Further, the game's COTS status made this study cost and time efficient. However, BigPharma still lacked some desired human-based activities, specifically good practice activities such as cleaning equipment. To address this shortcoming, a Python shell was developed and added to the interface. The shell acted to engage the player at predetermined times to complete worker-level tasks (termed worker tasks) (See Figure 1 and 2). Worker tasks presented themselves automatically while simultaneously pausing the BigPharma environment, at which point players could interact with the shell window (See Figure 1). Once complete, the task window automatically closed, and the BigPharma environment resumed. This design ensured the flow of the game was not interrupted and that players did not disengage with the virtual world due to the activity. Further, this design provides a flexible and seamless addition to the game. Indeed, editing the python shell (for example, using information obtained from FDA 483s) allows different real-life scenarios to be tested without the need for extensive programming.

By this design, the BigPharma/Python shell system (referred to as the game system) allowed players to interact with and express their strategies in a flexible but constrained virtual PMB. Furthermore, screen recording allowed the "capturing" of the player's strategies and actions within the game. In this way, the game system fulfills capturing human strategies in a pharmaceutical manufacturing setting, while also providing a sufficient level of fidelity in such a setting.

Figure 1 BigPharma gameplay with python shell (worker-level task) window. Shell windows were executed via Python 3-Juypter Notebooks scripts. Windows momentarily paused the game requiring input from the player before play could continue. Player's task decisions and in-game strategies were collected via program outputs and video-recordings respectively.

Defining Ethical Boundaries- What is Considered Cheating?

It is argued that the game system will be capable of capturing unethical techniques which bad actors can use to game the PSC. However, before this hypothesis can be tested what it means to be ethical or unethical within the game system must be defined. Clearly, "cheating" within the game would be unethical. But what exactly is cheating here? Treating the game space as a bounded environment then we may consider cheating as breaching said boundary. Here the game is bounded in two distinct ways, first, by the BigPharma and Python Shell code itself. That is the game embodies the rules and constructs what the player can and cannot do (Consalvo, 2009). For example, the player can make a capsule, but the player cannot make a spaceship (note that these rules also add to the virtual PMB fidelity). Secondly, the game's boundary is defined through external rules and objectives presented to players (guides that tell the player how to play and what to do). Hence, cheating would be breaking any rule embodied by the game itself (e.g., manipulating the game system's code) or breaking any external rules presented for the game. In this study, players were presented with rules and objectives at the beginning of each gaming session. Moreover, players were not given the opportunity to change the game's code. Hence cheating in this study will only concern defying the external rules given to the players. Which, in essence, means breaking any good practices. In this way, the development and deployment of the game system were complete. As such, we now possess a flexible virtual environment which

1. is capable of capturing human strategies and actions in a pharmaceutical manufacturing setting,
2. displays a sufficient level of fidelity in such a setting, and lastly,
3. has clearly defined ethical boundaries.

Next, set up and data collection for a series of experiments utilizing the above gaming system will be described.

Experimental Setup and Data Collection

The following hypotheses (1) a game system is capable of identifying the necessary rewards and penalties to ensure GMP compliance. (2) there are variables in the game that are predictive of real-life human-induced risks to the PSC, and (3) the game can capture unethical techniques which bad actors can use to produce counterfeit, adulterated, and misbranded drugs, were tested using a series of gaming sessions with various rules and objectives (RnO). RnO's were presented to players at the beginning of each gaming session through digital prompts. Prompts were developed using goal-setting theory's S.M.A.R.T criteria (See supplement information) (Doran, 1981). Further supplement information was provided to players to aid technical or logistical understanding where needed, for example, if the player was asked to make a specific drug. Then an example providing step-by-step instructions on how to make that drug in-game was given. All players were instructed to read through the prompt and supplement information before beginning a gaming session. Once beginning a session, players were asked to complete the session uninterrupted. Gaming sessions occurred in both remote and in-person settings. Players accessed BigPharma via PCs or Macs using the video game distribution service Steam (Valve Corporation, Washington, US). Jupyter Notebooks supported the python shell and recorded the players' decision-making regarding worker tasks. Furthermore, as mentioned, gaming sessions were screen recorded, and both recordings and shell (worker-level) decisions were collected.

Before starting observations, participants were trained on game mechanics via in-game tutorials and a common in-game challenge. This was done in order to ensure a minimum skill level at the onset of observations. In the next section, a series of metrics used to describe players' unethical behavior and strategies are described before presenting specific prompts.

Metrics

As described above, a python shell presents worker-level activities (termed worker tasks) not found within the BigPharma environment to players throughout their gameplay session. Each task contained both ethical and unethical approaches to completing them. The cost of the tasks (if conducted) is subtracted from the player's in-game currency. The specific worker tasks are summarized in Figure 2 and did not vary between prompts, a fact blinded to players.

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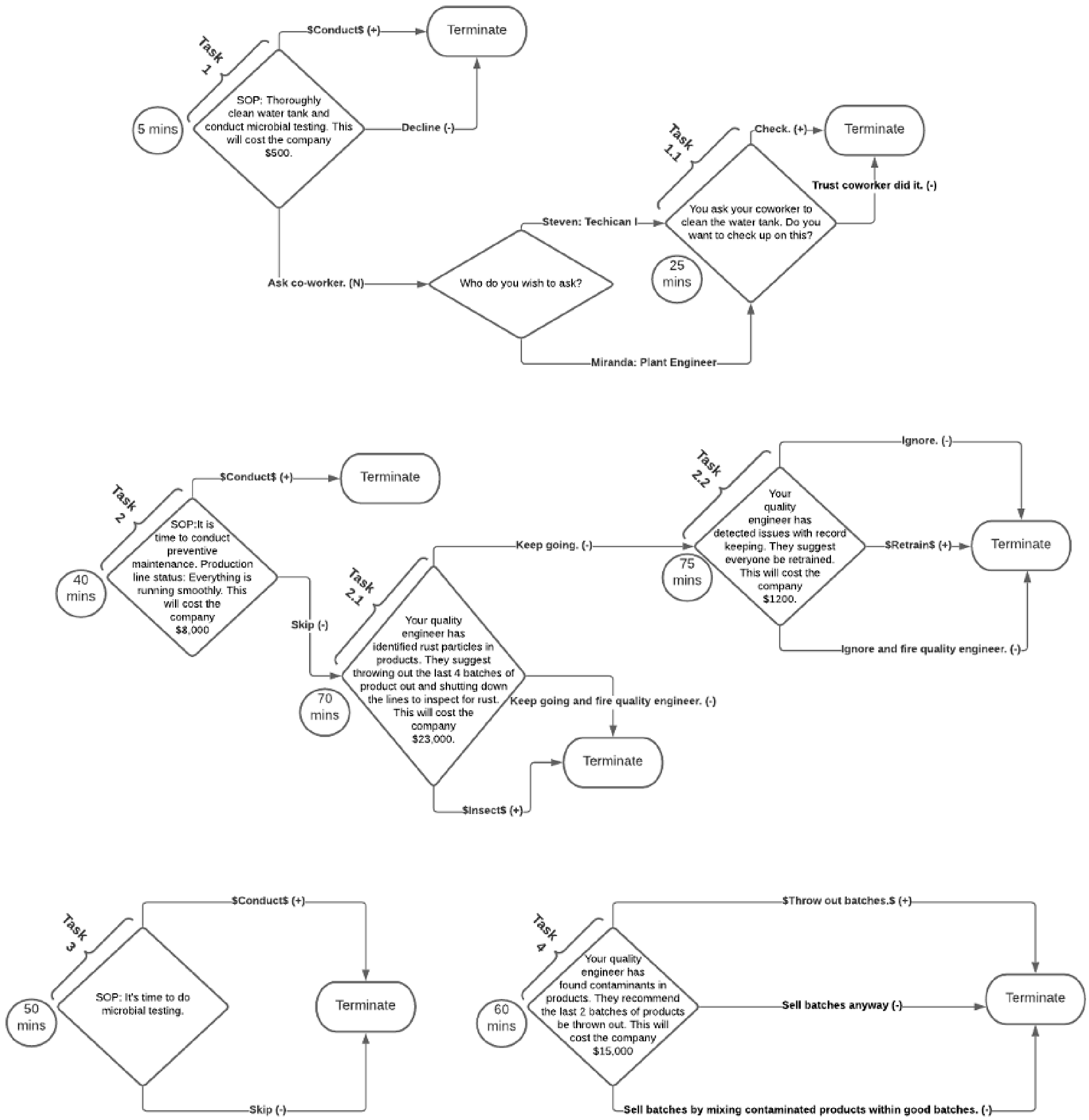

Figure 2 Decision trees describing the specific tasks presented to players. Where diamonds represent tasks, circles present specific time executions of respective task, and stadiums (the rectangles with rounded ends) represent the terminal points for the respective tree path. Both ethical and unethical choices were given to players for each task. Ethical choices cost the player in-game currency and are symbolized using $" option"$ and (+). In similar way unethical choices are identified by the use of (-).

Blinding was done by issuing new renamed files for each game session. The game file did not vary between prompts and was blinded in a similar fashion as above. Further altered loading screens reflected the session's particular prompt (See Figure 3) and worked to further blind players. That is (though blinded) all players throughout the study played the same BigPharma game file. This was done to reduce in-game variations.

Figure 3 Representative modified BigPharma loading screen (right) compared to original loading screen (left).

To describe the various unethical actions players were capable of executing two definitions were developed- Worker Fraud and Management Fraud. Worker fraud is defined as unethical decisions made when prompted to complete worker tasks (Figure 4). As mentioned, worker tasks were presented via a python shell and can generally be thought of as decisions made by workers in a PMB. The cost to conduct these tasks was subtracted from the game revenue, which the players were told before the start of each session. An example of worker fraud and its subsequent method of recording is illustrated in Figure 4.

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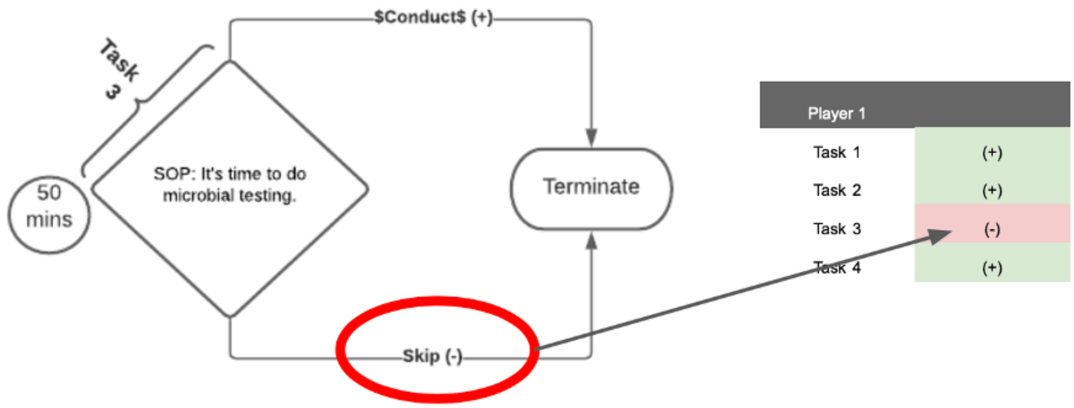

Figure 4 Worker Task 3 presents both an ethical and unethical approach to completion. Players' decisions are recorded through color coded tables. For this gaming session, Player 1 made ethical decisions in Tasks 1,2, and 4 represented by the green cells. For task 3 the player decided to skip the task. An unethical decision that is recorded by a red cell. Though not presented here, players' specific decision making may have resulted in unprompted tasks. In such a case the cells are blue and labeled accordingly as "null".

Worker fraud is quantified through a shell score (SS), where a player's shell score corresponds to the total number of worker tasks ethically completed. Hence a SS of 0 indicates a player took every shortcut; a SS of 1 means one task was performed ethically, a SS of 2 meant two tasks were performed ethically. Continuing to a SS of 7, indicating all tasks were completed ethically. When calculating the SS where applicable unprompted tasks (null-blue cells) are assumed to be ethically performed. Further, overall shell scores were calculated as the average or median of the players' shell scores across prompts.

Complementing worker fraud in describing players' actions is management fraud. Management fraud is defined as unethical practices done within the BigPharma environment. These actions are independent of the python shell and reflect decisions typically made by management—for example, deleting negative clinical test results. Management frauds are represented in two ways by categorical descriptors and an ethical score (ES). Categorical descriptors attempt to capture the frequency at which a particular unethical technique was used. These descriptors are selling subpotent drugs, concealing clinical results, selling unapproved drugs, using cheap/unapproved materials, and price hiking. See Categorical Descriptors for specific definitions.

Further describing management fraud is ethical scores (ES). ES attempt to provide a description and distinction of the various player management strategies and represent just how ethical each players strategy was. To designate ES,' players' specific actions were organized into timetables and labeled ethical or unethical (See supplement-Ethical Timetables). Using these tables players, overall strategies were described and compared against an ethical scale (see supplement-Ethical scale) to assign the players given ES. ES ranged from 0 to 5. Where an ES of 0 meant the player was utterly unethical (following no rules), ES of 1 was a very unethical strategy. Following guidelines when convenient. Only acting ethically when something was to be gained—for example, only maximizing drug potency when the maximum API concentration was the easiest to process. ES' of 2 meant the strategy was somewhat unethical. Indicating some ethical actions but mostly unethical behavior. 3's were somewhat ethical, following guidelines with some unethical actions. Or if acting unethically typically corrects the action. 4's represents a very ethical strategy—players with an ES of 4 followed guidelines moderately. Typically, breaking guidelines under exceptions (see supplemental information -Ethical Scale for details on exceptions). Lastly, an ES of 5 was completely ethical. Meaning the player followed all guidelines perfectly. The overall ethical score was calculated as the average or median of the players' ES' within prompts and labeled appropriately (See supplemental information-Shell and Ethical Scores, for exact values and computations).

The various prompts presented to players are described in the next section, followed by the results section.

Prompts

As mentioned above, to provide proof of the game system's utility, the following hypotheses (1) a game system is capable of identifying the necessary rewards and penalties to ensure GMP compliance. (2) there are variables in the game that are predictive of real-life human-induced risks to the PSC, and (3) the game can capture unethical techniques which bad actors can use to produce counterfeit, adulterated, and misbranded drugs, were tested using a series of video gaming sessions with various RnO. RnO's were presented to players at the beginning of each gaming session through digital prompts. This study consists of three primary prompts. Prompt 1 being profit centric. For this game, players were told to focus on making as much in-game revenue as possible while being approved to produce one and only one high-quality injectable drug. This prompt sought to test the hypothesis that in the absence of quality rewards, more unethical decisions would be made and was compared to a series of controls as well as Prompt 2 (quality-focused) and Prompt 3 (quality and profit-focused).

Three control (positive, negative, and random) games were compared with prompt 1, which presented players with a prefabricated process (see Figure 5). It should be noted that the prefabricated process was only given within the control games but theoretically was the process the players should have developed if they followed the rules (prompts) perfectly. While playing control games, players were asked not to alter the process but simply work with the marketing tab (adjust the drug’s price) while answering worker tasks entirely ethically in one game (positive control), entirely unethically in another game (negative control), and randomly for another (random control). Here a positive control represents producing a high-quality drug and making a reasonable profit. This is, in theory, following every guidance and standard operating procedure (SOP) perfectly. (Zero management or worker fraud). The negative control is the opposite of the positive control. It represents not following any SOPs or guidelines (should not produce a high-quality drug or be profitable, but it may be profitable or extremely profitable). (Complete worker fraud, Zero management fraud).

Figure 5 Virtual processing plant presented to players at beginning of gaming session in Prompt 1,2, and 3 (left) and control games (right).

Lastly, random controls were run. In this case, a random generator decided during the course of the game whether to follow a specific guidance or not. (Zero management fraud, Random worker fraud). Further, it should be noted that sometimes the Random control can outperform the Positive and the Negative controls. In such cases, running the random game over and over again and keeping the play with the highest profit can lead to new strategies for gameplay.

As mentioned, Prompt 2 players were quality motivated. In this game, players were asked to set profit aside and focus on completing a series of tasks by which they gained quality points. This prompt sought to test the hypothesis that when players are rewarded for quality, they would act increasingly more ethically. Lastly, Prompt 3 reintroduced profit motivates by asking players to maximize in-game revenue and quality points. This prompt sought to test the hypothesis that when players are rewarded for-profit and quality, they would continue to act ethically. Additionally, prompts 2 and 3 (like 1) clarified that players were to produce one and only one high-quality injectable drug.

Results

To provide proof for the value of a game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing setting, the following hypotheses are tested (1) a game system is capable of identifying the necessary rewards and penalties to ensure GMP compliance. (2) there are variables in the game that are predictive of real-life human-induced

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risks to the PSC, and (3) the game can capture unethical techniques which bad actors can use to produce counterfeit, adulterated, and misbranded drugs using a series of gaming sessions with varying RnOs. The first game- Prompt 1-was profit-focused and sought to prove that a higher frequency of unethical decision-making would occur when players are motivated by money. Prompt 2 was quality-focused and motivated players to gain quality points instead of money. This aim sought to prove that the players would make more ethical decisions when rewarded for quality. Lastly, Prompt 3 reintroduced monetary incentives while still rewarding quality. The results of these gaming sessions are characterized below using both cheating and profit metrics. Cheating metrics are split into two categories: worker and management frauds and aim to answer the following questions: How successful are you? And how much of that success is due to cheating? Done by 1) counting the number of ways in which players cheat, 2) counting the number of times that players cheat in each way. The profit metric wishes to answer -How much money does a player make by cheating? This is done by comparing players' in-game revenues. We begin the results with prompt 1 compared to the control games below.

Prompt 1 and Controls

N=4 (one female, three males) players played Prompt 1 in addition to three control games (positive, negative, and random). Players' total in-game revenue was calculated by subtracting costs of worker tasks (if conducted) from the players' end-game revenue (i.e., total at the end of gameplay). The total in-game revenue for Prompt 1 and controls, along with the players' ES' and ethical worker status, are presented in Figure 6.

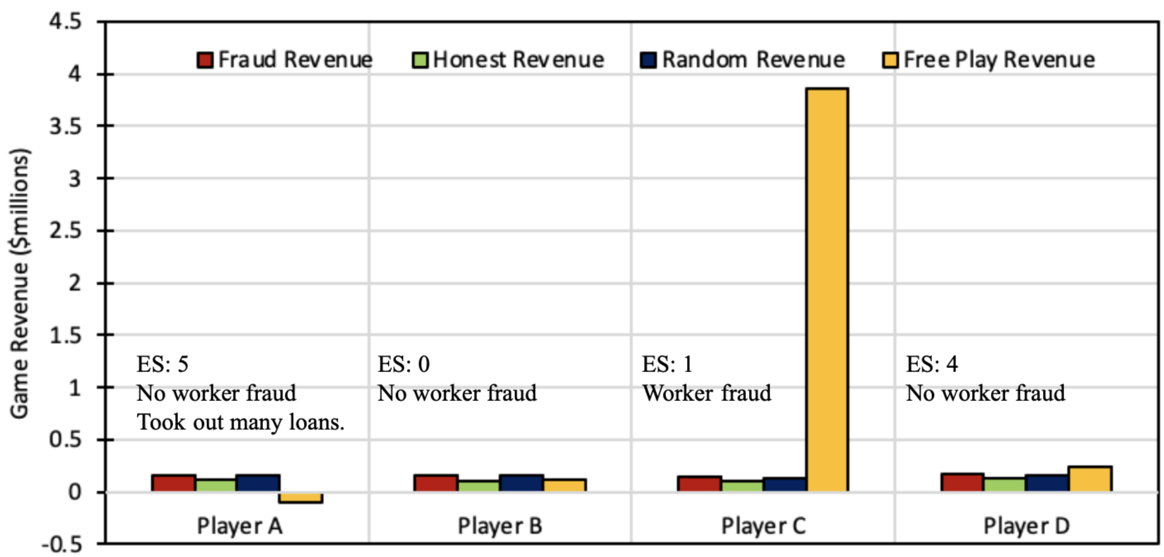

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Figure 6 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games. Where positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), random control data are in blue (Random revenue), and players' free play revenues are in yellow (Free-play revenue).

As can be inferred from Figure 6, the game is capable of capturing different strategies. Player A earned the least amount of in-game revenue but played the most ethical management strategy gaining an ES of 5 and completing all worker tasks ethically. Player B, like A, completed all worker tasks ethically (see Table 1). But Player B had the least ethical management strategy of the group earning an ES of 0. Despite this fact Player B did reasonably well, earning approximately the same in-game revenue as the positive control. Player C was the second most unethical earning an ES of 1. Unlike the other players, Player C did cut corners in the worker tasks. Performing several unethically (see Table 1). Interestingly Player C did the best by far in terms of in-game revenue. Lastly, Player D had a very ethical management strategy earning an ES of 4. And like Player A and B, Player D did not act unethically in worker tasks.

Table 1 Summary of player's and random generators worker task decisions for Prompt 1. Arrow points to the contingency table that quantifies the ethical vs unethical decisions for both the player and random generator.

Player ID	Task 1	Task 1.1	Task 2	Task 3	Task 4	Task 2.1	Task 2.2
Random A	(+)	(+)	(+)	(-)	(-)	null	null
Random B	(+)	null	(-)	(-)	(-)	(-)	(-)
Random C	(+)	(+)	(+)	(+)	(-)	null	null
Randomc D	(+)	null	(+)	(+)	(-)	null	null
Prompt 1							
Player A	(+)	null	(+)	(+)	(+)	null	null
Player B	(+)	null	(+)	(+)	(+)	null	null
Player C	(+)	null	(-)	(-)	(-)	(-)	(+)
Player D	(+)	null	(+)	(+)	(+)	null	null

	Unethical	Ethical	Total
Random Generator	9	11	20
Players	4	14	18
Total	13	25	

Momentarily omitting Player C, Figure 7 displays in greater resolution the game revenue comparisons of Players A, B, and D. Player A notably performed the worst, though Player A was the most ethical in both worker and management activities. Monitoring this Players' game reveals the player could have performed similarly to the positive control (honest revenue) if in-game loans were not frequently taken out, hinting that this player seemed to perform poorly on a business metric not measured in this study. Moving along, Player D did very well in terms

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of in-game revenue, outperforming positive, negative, and random control games with an ethical management strategy.

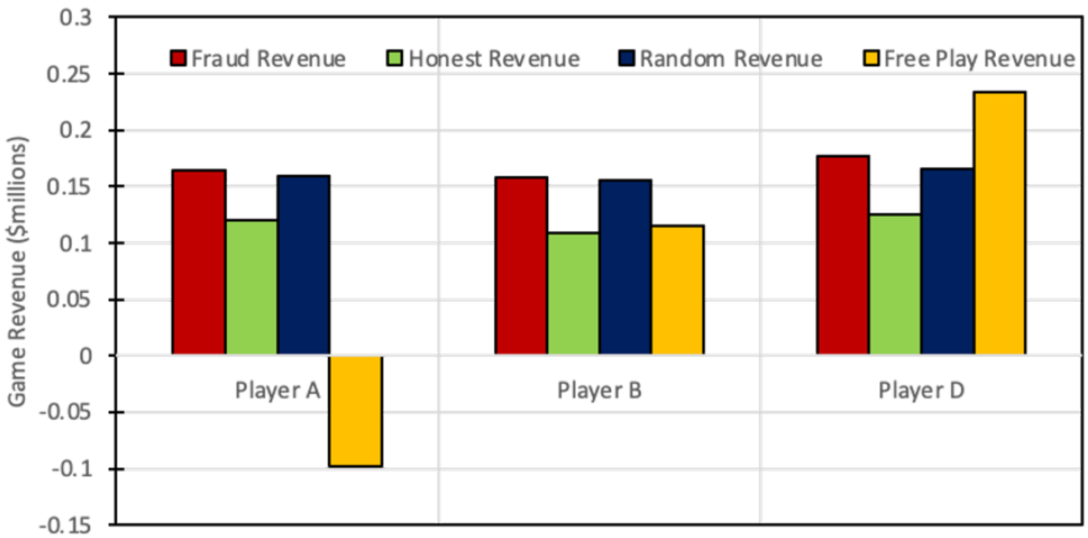

Figure 7 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games omitting Player C. Where positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), random control data are in blue (Random revenue), and players free play revenues are in yellow (Free-play revenue).

Further, from Figures 6 and 7, an interesting pattern emerges if a closer look is taken at Player B. Here Player B performed the most unethically in-game earning an ES of 0, meaning the player did not follow any of the rules provided to them. What makes a game, ironically enough, is the rules (Consalvo, 2009). Hence, by Player B's failure to follow any of the RnOs provided, Player B cannot be said to have played the present game. (Note Player C played a game unanticipated by the rules, but that is why we play the game, to detect those unanticipated events.) Indeed, monitoring of Player B's Prompt 1 gameplay shows the player did not make any high-quality injectable drug. Instead making cheap subpotent capsules and topical products. Given that the players were to produce one and only one high-quality injectable drug (with all the controls following this rule), it makes little sense to compare Player's B results with that of the controls, as the controls and Player B are truly playing two different games! Omitting Player B for this analysis produces Figure 8. Now the data suggest that (within our sample at least) a large positive deviation in revenue for Prompt 1 may be predictive of unethical behavior, providing support for the hypothesis that there are variables in the game that are predictive of real-life human-induced risks to the PSC. One such variable is profitability, and extreme profitability may be an indicator of danger to the PSC.

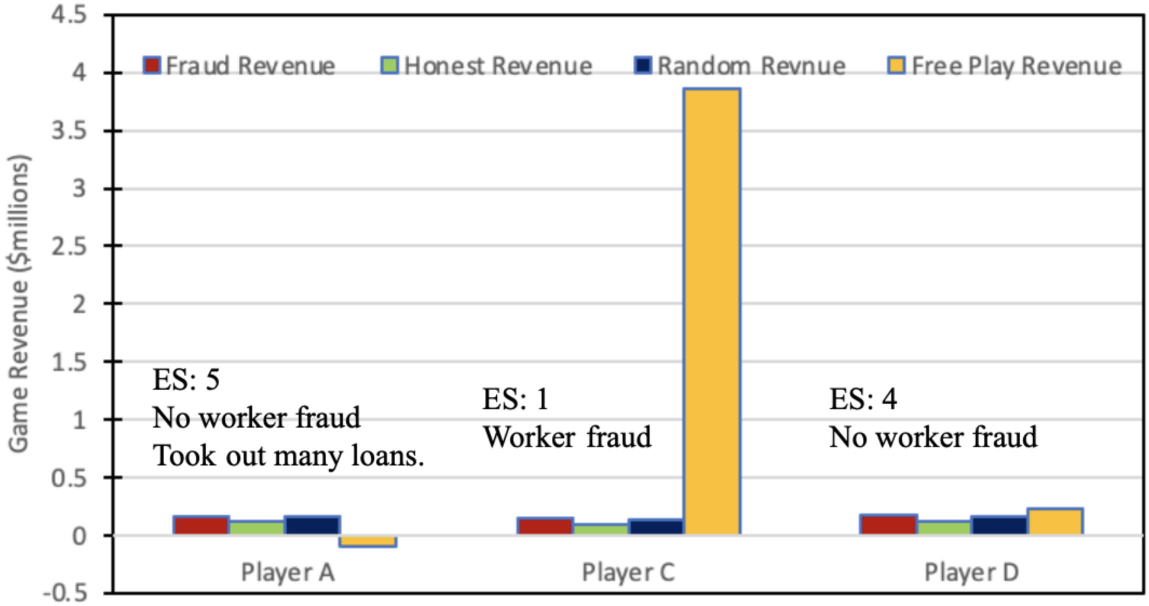

Figure 8 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games omitting Player B, who effectively played a different game. Positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), random control data are in blue (Random revenue), and players' free play revenues are in yellow (Free-play revenue).

Further extracting from this data set, a contingency table (see Table 1) was constructed comparing the players' Prompt 1 worker-level decisions to the random generator's decisions. As seen in Table 1, the random generator selected a total of 9 unethical choices out of 20 opportunities across players. On the other hand, players collectively acted unethically in a total of 4 out of 18 opportunities. An odds ratio was calculated from this data and determined to be 2.86 (random/player) (95% CI 0.69, 11.82), suggesting random selection was 2.86 times more likely to result in unethical choices than players. Though this result was not statistically significant at a 95% Cl it does suggest our players are acting rationally and not as random agents, and that our random agent leaned more towards unethical choices than our players (see supplemental information for the random generators source code). Indeed, our population tends to act ethically compared to flipping a coin in worker-level decisions.

Next, prompts 1,2, and 3 results will be presented along with a brief discussion.

Prompts 1,2, and 3. Will Quality Rewards Improve Behavior?

GxPs (Good "x" Practice, where x=manufacturing, clinical, distribution, etc.) are a set of accepted practices that are meant to limit risk and ensure high-quality products (Campbell and Lodder, 2021b). Nevertheless, as mentioned in the Introduction, some manufacturers choose to ignore and fail to follow GxPs, and the results can be devastating (Bates, 2012). PLI's may provide a solution to safeguarding patients by detecting CAMMS before they reach the patients. However, it is currently not feasible to screen every single drug at the pharmacy level, and current prioritizing models cannot account for new methods of cheating in the PSC. The DQG project aims to bridge this gap by showing that a useful game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing setting can be designed and deployed and used to simulate new methods of cheating in the PSC. In the previous sections, "Game System Design" and "Defining Ethical Boundaries-What is Cheating?" it was shown that such a game can be designed and deployed. To demonstrate the game's "usefulness," the following hypotheses were tested (1) a game system can identify necessary rewards and penalties to ensure GMP compliance. (2) there are variables in the game that are predictive of real-life human-induced risks to the PSC, and (3) the game can capture unethical techniques that bad actors can use to produce counterfeit, adulterated, and misbranded drugs. In section "Prompt 1 and Controls," we found data that suggests profitability may be predictive of unethical behavior, supporting the idea that there are variables in the game predictive of real-life human-induced risks to the PSC (hypothesis 2). Furthermore, we have already seen through sections "Metrics" and "Prompt 1 and Controls," that the gaming system could capture unethical techniques that bad actors can use to produce counterfeit, adulterated, and misbranded drugs (hypothesis 3). However, we have yet to test hypothesis 1 - that a game system can identify the necessary rewards and penalties to ensure GMP compliance. To test this hypothesis, we turn to a concept proposed by the FDA.

The FDA has conceptualized a quality scoring system that would score manufacturers based on their overall quality (e.g., GxP compliance). Within this framework, buyers would be given access to the manufacturer's quality score (Brennan, 2019), incentivizing manufacturers to achieve high scores to sell more products. A similar concept has been developed by Valisure, which seeks to develop an evidence-based quality score for drug products (Dabestani et al., 2020; Valisure, 2021a). Both the FDA and Valisure's concepts work off the school of the thought (SOT) that rewarding quality (by acknowledgement and transparency to buyers) will improve compliance. To test the effectiveness of this SOT in real-life would-be time consuming and expensive. But the DQG can provide both cost and time-efficient data on that SOT. To test the hypothesis that a game system is capable of identifying the necessary rewards and penalties to ensure GMP compliance, we introduced a quality reward in Prompt 2. Then in Prompt 3, we reintroduced profit motivations while continuing to reward quality. The results of these gaming sessions are shown beginning in Figure 9, which summarizes n=4 (one female, three male) player's in-game revenue, ES, and worker-level decisions.

Overall ES Average	2.58
Overall ES Median	3
Overall Shell Score- Average	6.5
Overall Shell Score- Median	7

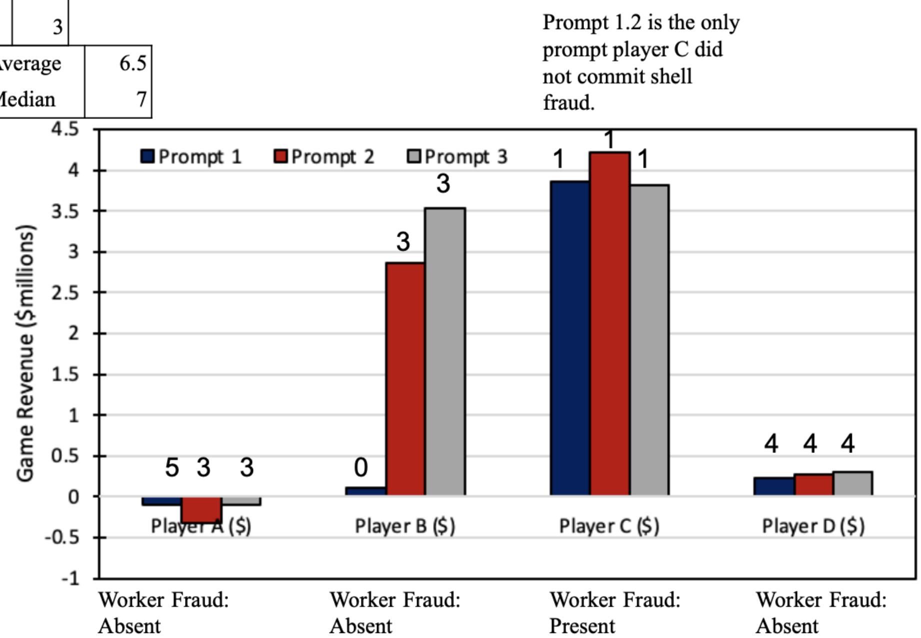

Figure 9 Summary of player's in-game revenue, ethical score (ES), and shell (worker-level) decision summary for Prompt 1 (blue bar), 2 (red bar), and 3 (grey bar). Ethical scores are presented over their corresponding bar. For example, Player B earned an ES of 3 in the Prompt 2 game. Further the overall and median ethical scores and shell scores across prompts are presented on the top left for reference. With the overall average ES being 2.58 with a median of 3. And the overall shell score average being 6.5 with a median of 7.

From Figure 9, we see that except for Player A, all player's in-game revenue improved from Prompt 1 to Prompt 2. This may be attributed to the quality motivation, as the players' submission order does not provide evidence of player skills (or ethics) improving with time (See Appendix 3-Improvement over Time? -A Glance at Players' Submission Orders, for more details). Quality was typically rewarded in the BigPharma game with higher sales, a variable directly dependent on the drug's "Cure Rating," which reflects the drug's quality and effectiveness.

However, cure-rating was not used as a metric in this study as it does not currently reflect reality (i.e., the cure-rating assumes consumer knowledge of the drugs' true quality and effectiveness, which is not the case in real-life). Nevertheless, it seems a natural assumption that drugs known to be of high quality will be bought more often than drugs known to be of lesser quality, as long as the prices are roughly equivalent. This quality concept lies at the heart of Valisure and Govzilla's initiative to develop a quality system for drugs (Valisure, 2021a). For this reason, the results in Figure 9 seem likely to carry over to a real-life setting. In addition, from

Figure 9, we see that except for Player A, ES either increased (such is the case for Player B) or remained consistent (Player C and D). Therefore, a closer look at Player A is warranted.

Looking deeper into Player A's gameplay, we see a player with an overall ethical management strategy reflective of high ES scores in addition to ethical worker-level decisions (i.e., all worker tasks completed ethically across all games). Yet, Player A's ES score drops two points from 5 in Prompt 1 (a profit-focused game) to 3 in Prompt 2 (a quality-focused game). And remains 3 in Prompt 3. After monitoring the gameplay (see Appendix 3-Ethical Timetables), we see that the player in Prompt 1 struggles to resist accepting loans that quickly drive them into debt. This strategy is seen in the Prompt 2 game as well. However, after suffering debt for nearly all of Prompt 1 and 2, the player quickly changes strategies in the middle of the prompt 2 game and begins selling subpotent drugs to turn a quick profit. These observations suggest that debt may be a driving force to unethical decision-making. Indeed, this assessment is backed by the criminology Fraud Triangle theory, which states that for fraud to occur, the agent must have the opportunity, ability to rationalize the action, and the pressure or motivation/incentive to act (Kassem and Higson, 2012). In the virtual PMB, the opportunity to commit fraud is readily available and easily rationalized. After all, "it is just a game". However, the pressure or motivation to cheat is questionable. It has been suggested that cheating in video games is often done to advance within the game (Consalvo, 2009; Doherty et al., 2014). This does seem to be the case for Player A, as debt constrains the player's ability to play. Indeed, players in debt within BigPharma cannot buy new equipment, research, or develop new processes, effectively stunting the player's in-game abilities. Interestingly enough, the Fraud Triangle theory readily identifies debt along with greed and addiction as an external pressure that can lead to fraud (AGA, 2015). Though difficult to say with certainty at this stage, Player A's switch from being completely ethical to cutting corners may reflect the virtual environments' ability to emulate real-life pressures.

Moving along to Player B, we see in Figure 8 that their ES score dramatically improved from 0 in Prompt 1, to 3 in Prompt 2. Meaning the player who previously failed to participate in the game presented to them was now actively playing with an ethical management strategy. Indeed, comments from the player confirm the improved stance towards the game- "I really enjoyed gaining the quality points." Player B's turnaround from completely unethical in Prompt 1 to ethical in Prompt 2 may be explained through incentive theory. Incentive theory suggests that human agents are motivated by incentives (Killeen, 1981). According to Killeen, incentives can be thought of as events that "generate a state of heightened arousal," increasing one's "vigor of ongoing behaviors". How long motivators can alter behavior and what magnitude the reward must be to alter one's behavior is still up for debate (Killeen, 1981; Korman et al., 1981). Nevertheless, the quality points introduced in Prompt 2 seem to have sufficed, motivating Player B to act more ethically. Along those same lines, it seems that the quality points were not sufficient to alter Player C and D's management strategy as their ES remained constant across prompts. However, a closer look at the frequency at which unethical techniques were used may shine a brighter light on the effectiveness of the quality points to incentivize players to play more ethically.

Table 2 summarized the number of occurrences at which an unethical technique was used by prompt. It can be seen that the introduction of a quality reward (Prompt 2) resulted in an overall decrease in unethical management practices. From 12 total occurrences in Prompt 1, to 8 total occurrences in Prompt 2 and 3. Further Table 3, summarizing the specific worker-level decisions, show a decrease in unethical decisions. Suggesting that in our population, the quality incentive seem to have increased players' ethos.

Table 2 Summarizes the number of occurrences at which an unethical technique was used by prompt.

Technique	Prompt 1	Prompt 2	Prompt 3	Total
Sold unapproved drug	3	2	1	6
Sold subpotent drugs	3	2	2	7
Used cheap/unapproved material	3	1	1	5
Conceal negative clinical results	0	0	0	0
Price Hike	3	3	4	10
Total	12	8	8	28

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Table 3 Summarizes Player's specific shell (worker-level) decision by prompt. Additionally, the average shell score and median per prompt is provided.

Player	A	B	C	D	
Prompt 1	Profit Focused				
Task 1	+	+	+	+	
Task 2	+	+	-	+	
Task 3	+	+	-	+	
Task 4	+	+	-	+	Shell Score Average: 5.75 Shell Score Median: 7
Task 2.1	null	null	-	null	
Task 2.2	null	null	+	null	
Prompt 2	Quality Focused				
Task 1	+	+	+	+	
Task 2	+	+	+	+	
Task 3	+	+	+	+	
Task 4	+	+	+	+	Shell Score Average: 7 Shell Score Median: 7
Task 2.1	null	null	null	null	
Task 2.2	null	null	null	null	
Prompt 3	Profit and Quality Focused				
Task 1	+	+	+	+	
Task 2	+	+	+	+	
Task 3	+	+	+	+	
Task 4	+	+	-	+	Shell Score Average: 6.75 Shell Score Median: 7
Task 2.1	Null	Null	Null	Null	
Task 2.2	Null	Null	Null	Null	

Additionally, from Table 2, we see that across Prompts 1, 2, and 3, that the top two most used unethical techniques were price hiking, occurring 10 times and selling subpotent drugs, which occurred 7 times. Looking closer at the players that sold subpotent drugs (see Table 4), we see that 100% of them sold their drugs above the median (27.5%) percent markup, aka price hiking. (See supplemental information for more on the definition and calculation of price hiking). Interpreting this suggests that the best quality at the lowest price may not just be a cheesy sales aid. As counterintuitive as these results may seem, it is indeed what has been observed in the DQS' Acetazolamide requested recall. Where the two companies providing subpotent medicine were selling substantially higher than the company that remained on the market. Further a study by Hu observed similar trends (high prices for low-quality drugs) when reviewing China's pricing and reimbursement policies (Hu and Mossialos, 2016).

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Table 4 Shows that of the players who sold subpotent drugs 100% of them simultaneously sold their drugs above the median (27.5%) percent markup aka price hiking. Here X's represent the player did commit the unethical technique, O's signify that the player did not commit the technique and E's represent the player did commit the unethical technique but under what was deemed an acceptable exception (See supplement information for more on these definitions).

	Prompt 1		Prompt 2		Prompt 3	
	Sold Subpotent	Price Hike	Sold Subpotent	Price Hike	Sold Subpotent	Price Hike
Player A	0	0	0	0	X	X
Player B	X	X	X	X	X	X
Player C	X	X	X	X	X	X
Player D	X	X	E	X	E	X

Lastly, a deeper look at the players' behavior in relation to the power level of their decisions is warranted. As stated, Worker frauds presented tasks to players generally representing worker-level decisions. Management frauds captured management-level decisions. Such things as price hiking and other activities are generally out of the hands of general workers. Studying Table 5 which summarizes the worker and management level frauds of each player, two trends emerged. First, the same players that acted unethically in worker-level actions also acted unethically in management-level activities (See Table 5). A predictable result if we consider Luke 16:10. Which states 10 "Whoever can be trusted with very little can also be trusted with much, and whoever is dishonest with very little will also be dishonest with much."

Table 5 Summarizes players' participation in worker and management fraud per prompt. Where red X's represent players' participation and O's represent players' restraint from that activity. See supplement information for collapsed versions of this table.

	Player A	Player B	Player C	Player D	
Management Fraud	0	X	X	X	
Worker Fraud	0	0	X	0	Prompt 1
Management Fraud	X	X	X	X	
Worker Fraud	0	0	0	0	Prompt 2

Management Fraud	X	X	X	X	
Worker Fraud	0	0	X	0	Prompt 3

The second trend emerging was not so straightforward. Players that acted ethically in worker-level tasks nearly always acted unethically at management-level tasks. Hence, the same person, depending on which role they were virtually playing, acted differently. In this case, Luke no longer holds. Nevertheless, this phenomenon can be captured in John Dalberg-Acton's famous quote. “Power tends to corrupt, and absolute power corrupts absolutely.” Suggesting that the effects of power are to blame. Indeed, John Dalberg-Acton's stance is no longer newsworthy and is amply supported by academic literature. Showing people in power to lie more often, undermine social relations, undervalue, and objectify others, possess less compassion, and act more cynical (Cislak et al., 2018; Inesi et al., 2012; Magnell, 2002; Wisse et al., 2019).

Conclusion

A system which rewards manufacturers for quality has been proposed to safeguard the PSC. However, testing this system in real-life would-be time and cost consuming. This study introduces a cost and time-effective method of investigating the quality reward strategy via a serious gaming system. Comparing a series of control games to the players' profit-motivated play, our population observed that a large positive deviation in-game revenue was predictive of both worker and management fraud. Suggesting that a company-profitability variable may be useful to integrate into current prioritizing risk models for drug scanning. Further through comparing a series of games, the first profit-motivated, the second quality-focused, and the last profit and quality-motivated valuable observations are made. First, the data suggest that a quality in-gaming strategy may improve players' ethical decision-making. Indeed, all players were 100% ethical in worker-level decisions gaining an average SS of 7 in their quality motivated play. Compared to the average SS of 5.75 recorded in profit-motivated management. After reintroducing profit in prompt 3, worker fraud, re-emerged but at a much lower frequency than present in prompt 1 (where quality rewards were absent)—yielding an overall SS of 6.75 in prompt 3 compared to 5.75. ES were used to reflect players' management strategies and were seen to improve moving from prompt 1 to 2. However, ES were consistent across the board, moving from prompt 2 to 3. Suggesting that after introducing quality rewards, profit did not corrupt or improve players' ethical decision-making. Though the current study is limited in sample size, it provides significant proof that serious gaming systems can provide valuable information to aid decision-makers. Furthermore, several observations presented in this study align well with behavior theories such as the Fraud Triangle Theory and power corruption.

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