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TOWARDS A HOLISTIC RISK MODEL FOR SAFEGUARDING THE PHARMACEUTICAL SUPPLY CHAIN: CAPTURING THE HUMAN-INDUCED RISK TO DRUG QUALITY

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TOWARDS A HOLISTIC RISK MODEL FOR SAFEGUARDING THE PHARMACEUTICAL SUPPLY CHAIN: CAPTURING THE HUMAN-INDUCED RISK TO DRUG QUALITY

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Pharmacy at the University of Kentucky

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ABSTRACT OF DISSERTATION

TOWARDS A HOLISTIC RISK MODEL FOR SAFEGUARDING THE PHARMACEUTICAL SUPPLY CHAIN: CAPTURING THE HUMAN-INDUCED RISK TO DRUG QUALITY

Counterfeit, adulterated, and misbranded medicines in the pharmaceutical supply chain (PSC) are a critical problem. Regulators charged with safeguarding the supply chain are facing shrinking resources for inspections while concurrently facing increasing demands posed by new drug products being manufactured at more sites in the US and abroad. To mitigate risk, the University of Kentucky (UK) Central Pharmacy Drug Quality Study (DQS) tests injectable drugs dispensed within the UK hospital. Using FT-NIR spectrometry coupled with machine learning techniques the team identifies and flags potentially contaminated drugs for further testing and possible removal from the pharmacy. Teams like the DQS are always working with limited equipment, time, and staffing resources. Scanning every vial immediately before use is infeasible 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 today. It doesn't let us predict what the risks will be in the future. To begin bridging this gap in predictive modeling capabilities the authors assert that models must incorporate the human element. A sister project to the DQS, the Drug Quality Game (DGC), enables humans and all of their unpredictability to be inserted into a virtual PSC.

The DQG approach was adopted as a means of capturing human creativity, imagination, and problem-solving skills. Current methods of prioritizing drug scans rely heavily on drug cost, sole-source status, warning letters, equipment and material specifications. However, humans, not machines, commit fraud. Given that even one defective drug product could have catastrophic consequences this project will improve risk-based modeling by equipping future models to identify and incorporate human-induced risks, expanding the overall landscape of risk-based modeling.

This exploratory study tested the following hypotheses (1) a useful game system able to simulate real-life humans and their actions in a pharmaceutical manufacturing

process can be designed and deployed, (2) there are variables in the game that are predictive of human-induced risks to the PSC, and (3) the game can identify ways in which bad actors can “game the system” (GTS) to produce counterfeit, adulterated, and misbranded drugs.

A commercial-off-the-shelf (COTS) game, BigPharma, was used as the basis of a game system able to simulate the human subjects and their actions in a pharmaceutical manufacturing process. BigPharma was selected as it provides a low-cost, time-efficient virtual environment that captures the major elements of a pharmaceutical business-research, marketing, and manufacturing/processing. Running Big Pharma with a Python shell enables researchers to implement specific GxP-related tasks (Good x Practice, where x=Manufacturing, Clinical, Research, etc.) not provided in the COTS BigPharma game. Results from players' interaction with the Python shell/Big Pharma environment suggest that the game can identify both variables predictive of human-induced risks to the PSC and ways in which bad actors may GTS. For example, company profitability emerged as one variable predictive of successful GTS. Player's unethical in-game techniques matched well with observations seen within the DQS.

KEYWORDS: serious gaming, drug quality, pharmaceutical manufacturing

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DEDICATION

To God, friends, and family.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

GLOSSARY

Active pharmaceutical ingredient – Ingredient which is known to deliver the desired therapeutic activity.

BigPharma environment – Refers to the BigPharma videogame alone. Excludes the python shell additions.

Categorical Describers – A collection of management level actions and their definition. See Appendix 3 for each action its respective definition.

Combination therapy or drug – A drug which treats two or more illnesses.

Ethical scale – Rubric used for assigning players ethical score value.

Ethical score – A numerical value which provides a description and distinction of the various player management strategies and represent just how ethical the strategy was.

Ethical Timetable – Tables which organize players important actions during gameplay via time of action. These are constructed using the players screen recordings of their gaming session.

Excipients – Additional ingredients within a drug formulation which are not the API. Examples include stabilizing polymers, surfactants, etc.

Fidelity – A concept which describes the level of representation or accordance with reality within the game (Lukosch et al., 2019).

Fraud – Represents any deceitful, unethical or unaccepted decision or behavior.

Gameplay session or gaming session- From the time the player starts playing a game to the end.

Management fraud – unethical practices done by players within the BigPharma environment.

PC- Computer with a Windows operating system.

Pharmacy – Business or Institution which distributes drug products to patients or consumers.

Pharmacy level investigators – Pharmacies which analytically test their drugs through infrared spectrometry techniques or other advanced methods to inspect the quality of a drug product.

Prompt 1 – The first game played by players. For this game players main objective was to make the most profit as possible.

Prompt 1.0.2 – An adjusted version of the prompt 1 game. This game adjusted the costs of worker level tasks.

Prompt 1.2.1 – An adjusted version of prompt 2. This game updated language in the quality rubric.

Prompt 2– The second game played by players. For this game players main objective was to collect all the quality points.

Prompt 3 - A game played by players. For this game players main objective was to collect all the quality points and gain as much profit as possible.

Python Shell – Integrated for the python 3 script. Allows for the launching of code and for the worker level decisions to be collected.

Quality drug – A drug which consistently delivers the desired therapeutic effects (Woodcock, 2019a) and is produced incompliance with good practices.

Shell score – A numerical value used to quantify Worker fraud. Value represents the number of worker tasks completed ethically.

Subpotent drug – A pharmaceutical drug product that does not possess the labeled amount of active pharmaceutical ingredient.

Worker fraud- unethical decisions made when prompted to complete worker tasks.

Worker tasks – A collection of activates presented through the python sell. Players completed these tasks through a task window.

Worker tasks cost – Represents the various amounts of in-game currency the player subtracts from their earned revenue for each ethically completed worker task. Each task varied in cost.

ABBREVIATIONS

Absorption, Distribution, Metabolism, and Excretion (ADME)

Active pharmaceutical ingredient (API)

Algorithmic game theory (AGT)

Algorithmic mechanism designs (AMD)

Angiotensin II receptor blockers (ARB's)

Artificial intelligence (AI)

Artificial neural network (ANN)

Attention deficit hyperactivity disorder (ADHD)

Behavioral game theory (BGT)

Burkholderia cepacia (BC)

Commercial off the self (COTS)

Computational fluid dynamic (CFD)

Continual reassessment method (CRM)

Counterfeit, adulterated, and/or misbranded medicine (CAMM)

Current good manufacturing practices (cGMPs)

Cyclodextrin (BCD)

Deep learning (DL)

Dimethylformamide (DMF)

Drug development process (DDP).

Drug Quality Game (DQG)

Drug Quality Study (DQS)

Ethical Score (ES)

European Union (EU)

Federal Food and Drug Administration (FDA)

Fiscal year (FY)

Fit-for-purpose (FFP)

Free energy perturbation (FEB)

Generative Adversarial Networks (GANs)

GlaxoSmithKlines (GSK)

Machine learning (ML)

Maximum tolerated dose (MTD

Molecular modeling (MD)

N-nitrosodimethylamine (NDMA),

New drug application (NDA).

Official action indicated (OAI)

On-the-ground (OTG)

Over-the-counter (OTC)

Personal computer (PC)

Pharmaceutical manufacturing business (PMB)

Pharmaceutical supply chain (PSC)

Pharmacodynamic (PD)

Pharmacokinetic (PK)

Pharmacy level investigators (PLIs)

Poisson– Boltzmann surface area (MM/PBSA)

Quantitative structure-activity relationship (QSAR)

Reducing mean tumor diameter (MTD)

Reinforcement learning (RL)

Rules and objectives (RnO)

Shell Score (SS)

Site-selection model (SSM)

Stag hunt (SH)

Standard operating procedure (SOP)

Traditional game theory (TGT)

United States Government Accountability Office (GAO)

United States of America (US)

University of Kentucky (UK)

Voluntary Action Indicated (VAI)

World health organization (WHO)

CHAPTER 1. INTRODUCTION

The pharmaceutical industry is unique in that customers are also patients. Hence, there is zero room for error in the design, manufacturing, and distribution of pharmaceutical products. Indeed, even seemingly minor defects or delays in other product sectors can be devastating in the pharmaceutical industry (Miller, 2011). Despite the highly sensitive nature of pharmaceutics, the pharmaceutical supply chain (PSC) is vulnerable. Indeed, the US. PSC has often faced drug shortages, with the COVID-19 pandemic only exacerbating the problem (Bookwalter, 2021; Lee Ventola, 2011). Vulnerabilities in the PSC are at least partly due to the PSC complex and global nature. To illustrate the level of complexity involved in the PSC, consider a single hypothetical capsule. One capsule product requires the active pharmaceutical ingredient (API), excipients, and the capsule itself. Each of these ingredients is likely sole-sourced by an individual company to the product maker. Assuming the drug product only required one excipient (nearly never the case), we already have four companies involved, excluding the transporters. Indeed, a very conservative amount as some companies could be supplied by hundreds of suppliers (Challener, 2014; Singh, 2016). The number of companies only grows increasingly large after producing the drug product as the capsule will find its way through wholesale distributors, secondary wholesalers, and more transporters before landing in pharmacies. Further, each company may be located in entirely different geographical regions. Though this example simplifies the production and distribution of a single capsule, it should provide context for the reader on how supply shortages can arise. For example, if the API supplier were to encounter a natural disaster that slowed production, a ripple effect may be observed. With the API source stalled, the capsule production must decrease while the demand remains the same

or greater. Another and equally important-though not as obvious- issue that arises within the PSC is the number of people (agents) involved. Just as much as the PSC is a complex technical network, it is a social system. Moreover, for the PSC to be successful (e.g., no drug shortages and high-drug quality), agents must cooperate. However, for cooperation to exist, trust must be present.

Trust reduces uncertainty in the future and allows for cooperation (Bachmann, 2001). Indeed the uncertainty of a trustor can be reduced concerning the trustee's future actions (Hardin, 2002). Trust allows us humans (or agents) to have more certainty in our future and rely on others. Setting contracts and legal agreements aside (which do provide extra insurance for the future), trust allows agents of the PSC to cooperate for the benefit of themselves and the patients. PSC agents typically do well cooperating with one another and patients (if they did not, we could imagine a world without easily accessible medicine). However, some have used the highly technical and socially complex environment to deceive others and collect ill-gotten gains.

Some PSC agents cut corners on standard practices (e.g., FDA's good practices) while others outright cheat the system (Bates, 2012; Eban, 2019a). For example, Bates accounts a real-life story of how a private investigate easily bought substandard medicine while also being advised on how to resell them to the public. According to Bates, the seller recommended mixing the substandard medicine with a good batch at a rate of approximately 25 percent (Bates, 2012). Such behavior leave patients comprised since detecting counterfeit, adulterated, or misbranded medicine (CAMMs) is nearly impossible without specialized equipment and advanced analysis (Galante et al., 1992). It has been proposed that pharmacy-level investigators (PLIs) could provide a much-needed on-the-

ground inspection for patients. Indeed, Valisure and the University of Kentucky (UK) pharmacies have flagged numerous CAMMs (Fiore, 2021; Valisure, 2019a). However, PLI's on-the-ground status often means working with limited equipment and staffing resources. Admittedly, risk scoring models are often used to prioritize drug scanning (similar to the models also used by the Federal Food and Drug Administration (FDA) to prioritize on-site inspections-See Chapter 2). However, risk scoring models can only inform PLI's or the FDA on what should be checked today. Such models speak nothing to the future. This limitation is because traditional models are trained based on historic knowledge.

Even the most sophisticated predictive models can only account for information days or weeks in the past. A model that could account for unforeseen or novel behavior would be more helpful for PLI's, and agencies such as the FDA to stay one step ahead of deceitful PSC agents. For such a model to exist, it would need the capabilities of capturing the human element (imagination, creativity, and more) and all its unpredictability. A serious digital gaming system is well equipped for this task. Indeed, games have been capturing human strategies for decades in warfare. For example, the Prussian military developed the game Kriegspiel and is on record as being used by the Japanese navy in the Russo-Japanese war of 1904-1905 (Favini, 2010). Years later, games are still being used regularly to find optimal strategies (Axelrod, 1984). Further, digital games are being used to capture human imagination and creativity to solve scientific problems. For example, the online game Foldit which allows players to fold proteins like a puzzle, provided insights that solved the crystal structure of M-PMV retroviral protease, an enzyme involved in reproducing HIV in just three weeks (Khatib et al., 2011).

In this project, a serious gaming system is designed and deployed to capture players' imagination and creativity when it comes to cheating the PSC. Specifically, the project investigates if rewarding players for tasks attributed to quality will decrease the use of unethical or deceitful behavior. Before diving in, a brief review of the PSC current line of defense is given before providing more information on gaming in both theory and problem-solving.

CHAPTER 2. CURRENT LINE OF DEFENSE: FDA'S METHODS TOOLS FOR SAFEGUARDING THE HUMAN DRUG SUPPLY

2.1 Introduction

Visually detecting adulterated, defective, or contaminated pharmaceuticals is nearly impossible (beyond cosmetic defects like a cracked vial). Instead, specialized and often destructive analytical techniques such as liquid chromatography and mass spectrometry must be used to identify adulterated products (Nikolin et al., 2004). For this reason, pharmacists can unintentionally dispense CAMMs to patients. Simply put, bad drugs can lead to bad outcomes. Patients may experience loss of therapeutic benefits, become ill, and, in extreme cases, death. To ensure drug quality, pharmaceutical manufacturers execute quality control and other current good manufacturing practices (cGMP). cGMP is among the GxPs, or Good "x" family of guidelines, where x is manufacturing, laboratory, research, engineering, documentation, etc. These guidelines are created collaboratively by agencies such as the US Food and Drug Administration (FDA) and the Global International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). GxP guidelines are intended to provide accountability and traceability to the "x" activity. cGMP itself generally refers to the requirements outlined in the Federal Food, Drug, and Cosmetic Act of 1998 (FD&C Act), Section 501(a)(2)(B). It is generally accepted that by following cGMPs, undesirable events will be mitigated. However, following cGMP does not provide a guarantee against substandard drugs. Further, many manufacturers fail to meet cGMP standards at all (Campbell and Lodder, 2021a).

The FD&C Act requirement for drug manufacturers to follow cGMP is enforceable by the FDA (FDA, 2016a; "Federal Food, Drug, and Cosmetic Act ß501(a)(2)(B), 21 U.S.C. ß351," 1998). Despite this, many manufacturers still fail to meet cGMP standards.

Lack of compliance is often unintentional; however, sometimes deliberate fraud occurs (Campbell and Lodder, 2021a; Eban, 2019a; Evana et al., 2019; Mu and Carroll, 2016; Okoye and Nwoka, 2019). Regardless of the intent, manufacturers failing to meet cGMP standards have occupied FDA inspectors for decades. To combat threats to the PSC the FDA now conducts quality testing of products and perform on-site inspections of drug manufacturing firms. However, with limited resources, the FDA has struggled to keep up with the demands. By the end of the fiscal year (FY) of 2019, the number of drug manufacturing sites worldwide totaled 4,273, down 8.6% from the previous year (FDA, 2020a). Yet only 1,258 drug quality surveillance inspections were conducted of these firms. For data regarding the number of on-site inspections conducted, the FDA provides a database that may be reviewed at

https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=oip&status=public&id=OIP-Number-of-inspections-completed-in-country-by commodity&fy=2020.

Further, the FDA relied on European Union (EU) regulators under the Mutual Recognition Agreement to conduct 109 drug quality inspections in the EU region (FDA, 2020a; FDA and EU, 2017). Despite the decrease in total manufacturing sites and reliance on EU regulators, the FDA reported a decrease of more than 4% in annual domestic on-site inspections performed over two years (FY17-19) (FDA, 2020a). On the other hand, more than a 6% increase in on-site inspections in India was reported. However, the total percentage of foreign manufacturers decreased from 61% to 58% from FY2018 to FY2019. Hence, it seems the FDA may lack the necessary resources to frequently inspect domestic and foreign drug manufacturing sites (FDA, 2019, 2020a).

The reasoning behind FDA's reduced inspections was briefly alluded to by the organization in response to the United States Government Accountability Office (GAO) preliminary findings of the FDA's performance (Denigan-Macauley, 2019). In a report released by GAO (GAO-20-262T), a testimony before the Subcommittee on Oversight and Investigations, the Committee on Energy and Commerce, and the US House of Representatives, the organization outlined that between the FYs of 2016 and 2018, both foreign and domestic inspections decreased by approximately 10% and 13% respectively. In response, the FDA attributed the decrease to job vacancies, claiming that in June of 2018, the FDA employed 190 investigators capable of conducting foreign inspections, but by November, the FDA had 58 vacancies (Denigan-Macauley, 2019). Given this explanation suggest that the FDA is facing staffing shortages.

Facing shrinking resources and persistent demand, the FDA relies now more than ever on state-of-the-art tools to effectively redistribute the available workforce. Applying today's technology to computable tasks allows human workers to focus on and more adequately tackle the complex intricacies of the pharmaceutical supply chain (PSC). Proper redistribution of the FDA's workforce could help increase the identification and elimination of potential threats to the PSC.

This chatper provides a brief review of the FDA's current methods. The section "Risk-Based Site Selection" focuses on the FDA's site-selection model (SSM) for on-site inspections. The section "Analytical Testing" provides a brief description of the FDA's role in drug quality testing. Finally, a brief description of tools and campaigns developed to educate both consumers and supply chain personnel regarding risk in distributing and purchasing medicine is discussed.

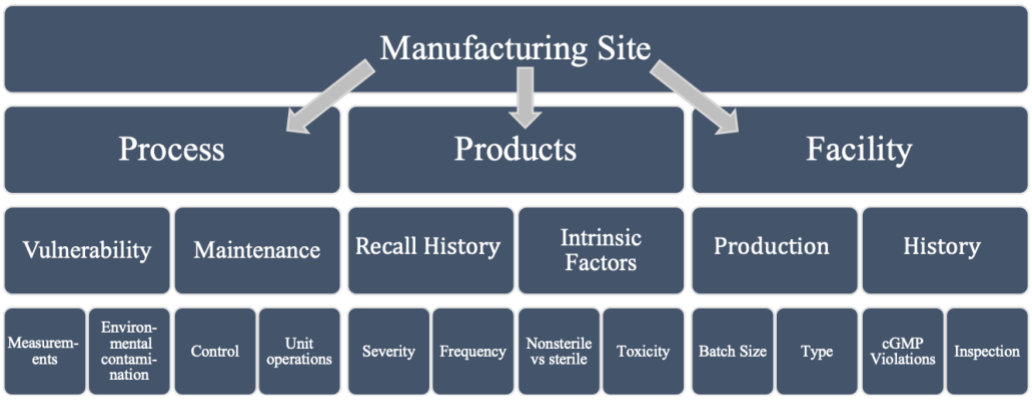

Figure 2.1 Representative conceptual layout of FDA's risk-based site-selection model (SSM). Where the model theoretically inputs a manufacturing site to be analyzed in terms of risk factors. Beginning by dividing the site into three general groups: Process, Products, and Facility. Further division of these general groups then takes place. Breaking each group into categories of risk, such as product recall history. Once a site's relevant characteristics are deconstructed into risk categories, risk-factors are then itemized. Examples of risk factors include a facility's production type (e.g., packing facility, API production, labeling facility) and process hazards such as environmental contaminants (e.g., the process using significant amounts of hazardous material). Each risk factor contributes to a weighted risk potential for each general group (FDA, 2004a).The estimated combined risk potential for the site is then calculated through a linear combination of these groups (FDA, 2004a). Hierarchical map modified from (FDA, 2004a).

2.2 Prioritizing Inspections: A Risk-Based Site-Selection Model

On-site inspections are intended to verify a manufacturing firm’s compliance with cGMP. The basis for cGMP can be found in the Code of Federal Regulations -

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211. As outlined in the FD&C Act, domestic drug manufacturing firms must be inspected at least once every two years. However, fulfilling this requirement has proven difficult since the establishment of the FD&C Act in 1998. This may be partially due to the globalization and increased complexities of the PSC (Singh, 2016). Indeed, most drug manufacturing firms are now located overseas (Baldwin, 2012; FDA, 2017a, 2019; Woodcock, 2019b). Lacking the necessary resources, the FDA was unable to keep the FD&C Act requirement. Failing to conduct biennial inspections of domestic drug firms, the FDA responded by introducing a risk-based site-selection model in the FY2005 (CDER, 2018). The model is an outcome of the FDA's pharmaceutical cGMPs for the 21st-century initiative that was first announced in 2002 (FDA, 2004b). The initiative aimed to ensure FDA policies and actions were risk-based and scientifically backed. Developed through expert opinion, recall history, and other FDA records, the risk-based SSM helps prioritize manufacturing sites for inspection.

The SSM was developed through what the FDA describes as a "multi-step analytical process," which consists of (1) hazard identification, (2) conceptual modeling, (3) risk estimation, and (4) risk filtering (FDA, 2004a). Hazard identification was conducted by gathering qualitative data from experts in fields such as investigative inspection. These experts were then asked to answer questions such as “In your experience, what are the principal factors important in predicting adverse impacts to drug quality?” and then asked follow-up questions such as “What variables are associated with, or predictive of, those hazards?” (FDA, 2004a). This step was intended to be an initial brainstorming stage and identified 70 potential risk factors (FDA, 2004a). Next, the potential risk factors were

filtered, eliminating duplicates and those difficult to quantify. With the remaining risk factors, a conceptual model was constructed. Organized by FDA personnel, risk factors were connected based on generality and relationship. The resulting conceptual framework is summarized in Figure 2.1.

Examining Figure 2.1, the SSM analyzes a manufacturing site in terms of risk factors. The model first divides a manufacturing site into three general groups: Process, Products, and Facility. Further division of these groups then takes place. Breaking each group into categories of risk, such as product recall history. Once a site's relevant characteristics are deconstructed into risk categories, risk factors are then listed out. Risk factors include a facility's production type (e.g., packing facility, API production, labeling facility) and process hazards (e.g., the process using significant amounts of hazardous material). Each risk factor can be thought to contribute to a weighted risk potential for each of the general groups (Process, Products, and Facility) (FDA, 2004a). That is the risk potential for each general group is a combination of the weighted risk factors. The estimated combined risk potential for the site is calculated through a linear combination of these groups (FDA, 2004a). Although the pilot SSM's exact algorithm has not been released, it may be assumed from documents provided by the FDA that the linear combination takes on a form similar to that illustrated through Equations 1and 2. By allowing the column vector $\vec{v}_{i,j}$ to represent risk factor i belonging to group j (e.g., Process, Products, or Facility) for site k and by assuming that the assignment of the $w_{i,j}th$ weight factor corresponds to the $v_{i,j}th$ risk factor, then the combined weighted risk factors for group j can be thought to take the form of Equation 2.1.

$$\vec{w}_{i,j} * \vec{v}_{i,j} = R_j \text{ Equation 2.1}$$

Where, $\vec{w}_{i,j}$ is the row vector representation of weight factors, corresponding to risk factors with the column vector $\vec{v}_{i,j}$. Then R_j represents the mathematical combination of weighted risk factors belonging to group j (Process, Products, or Facility). It should be noted that the weighted risk factors are numerically discrete values and the weight factor assigned to select risk factors are determined by expert opinion, empirical evidence or a mixture of both (FDA, 2004a).

Lastly, the potential risk of site k is given by linearly combining R_j for each group and can be thought of as taking the form of Equation 2.2.

$$aR_1 + bR_2 + cR_3 = R_k \quad \text{Equation 2.2}$$

Where a, b, c are scalar constants and $R_{1,2,3}$ is R_j with $j = 1,2,3$ representing the Process, Products and Facility group respectively. Then the output of this model is a numerical value R_k representing site $k's$ risk potential based upon the linear combination of groups R_j. A simple python script is provided to illustrate the model (an Octave script can be provided upon request). Type in some test numbers and see how these equations act.

https://colab.research.google.com/drive/1A1DZ1ExxhsJjG2Wbj6zbW74pNg7yhcsl?usp=sharing

In essence, the SSM model attempts to represent a manufacturer's potential failure through mathematically combining weighted risk factors into one numerical value (e.g., R_k). This score is then thought to be used to prioritize on-site inspections. That is given a

scenario where manufacturer A is more likely to produce suboptimal drug products than manufacturer B according to the respective R_k scores. Then manufacturer A will be prioritized for on-site inspection by the FDA over manufacturer B. Allowing FDA investigators to focus their efforts on high-risk sites.

2.3 Analytical Approach

Pharmaceutical manufacturing requires among the highest quality standards of any industry. However, batch to batch and sometimes item to item variation is an inescapable element of process manufacturing (Xie and Schenkendorf, 2019). To mitigate the risk to product quality introduced by these inconsistencies, drug manufacturers are tasked with validation activities such as testing batches to ensure high-quality production is maintained (e.g., a product free from contaminants and reproducibly delivers the therapeutic benefit described on the label Woodcock, 2004). Despite this requirement, impurities are not always identified before distribution. Such events occur in other types of manufacturing, such as food, where a defective fruit, for example, may slip into distribution. However, this is typically less of an issue, given that a defective orange can be inspected at the consumer level for quality. This is not the case for drug products where visual detection of CAMMs is nearly impossible. Instead, specialized equipment must be used that the everyday patient does not have access to, such as infrared spectrometry (Galante et al., 1990). Hence, the FDA must conduct quality testing for patients. In FY2019, FDA laboratories analyzed nearly 734 drug samples (FDA, 2020a). Included in the drugs tested was Valsartan, a common blood pressure medication. After receiving notice that Valsartan was potentially contaminated with N-nitrosodimethylamine (NDMA), an impurity with potential carcinogenic properties (Mahase, 2019; Pottegård et al., 2018) The FDA responded by developing a method to detect and quantify NDMA and other nitrosamine impurities in

angiotensin II receptor blockers (ARB's) (FDA, 2020a). Valsartan was then tested for NDMA in FDA laboratories, where the initial claims were confirmed. These results prompted a recall of many ARB's in the US, including Valsartan, Losartan, Irbesartan, and Olmesartan (Farrukh et al., 2019). Following this recall, in June 2019, NDMA was found in Ranitidine by Valisure, an online pharmacy that tests each batch of products before disturbing to customers (Valisure, 2019a). In response, the FDA again developed a method to detect and quantify NDMA in Ranitidine. In total, the FDA for the FY2019 would develop methods to detect and quantify eight different types of nitrosamines for ten different drugs that year (FDA, 2020a). In response to the seemingly sudden uptake in nitrosamine impurities, the FDA sent out 23 investigators globally to investigate sites related to the recalls, of which 61% of whom received a report of OAI or official action indicated—suggesting that many of the sites affected by the recalls were not in full compliance with cGMP (FDA, 2020a). However, there are indicators that using the solvent dimethylformamide (DMF) in synthesizing the API in Valsartan's case, is to blame (Parr and Joseph, 2019). Further, DMF is classified as a Group 2A probable human carcinogen by the World Health Organization (WHO) and the International Association for Research of Cancer (IARC) (Society, 2019). Despite this, the FDA deemed 8,800,000 nanograms safe for daily intake limits; this prompted Valisure in June 2019 to issue a citizen's petition to the FDA, requesting lower daily intake limits of DMF and a recall of all Valsartan processed with this solvent. The citizen petition submitted by Valisure can be reviewed here: https://www.regulations.gov/document?D=FDA-2019-P-2869-0001.

Given that arguably the two most extensive recalls in the past couple of years have been initiated by Valisure and not the FDA, it seems the FDA may benefit from aid in drug

surveillance. Fortunately, Valisure has inspired other quality testing pharmacies to emerge, such as the University of Kentucky (UK) Central Pharmacy. Here, the injectable medication used within the UK's hospital is undergoing quality testing. Similar quality testing sites will likely begin to appear as more recalls and safety alerts result from such work. Collaboration between the FDA and these "second check" pharmacies will be critical for optimized drug quality testing. Another tactic to catch faulty batches of drugs is to use patient and physician reports. This topic will be touched on in the next section.

2.4 Consumer Tools

In addition to providing guidelines, on-site inspections, and quality analysis testing, the FDA also provides tools for patients and physicians to participate in drug surveillance. *MedWatch* is an online tool that allows patients, doctors, and consumers to voluntarily report potential risks to the FDA (FDA, 2020b). *MedWatch* accepts reports regarding prescription and over-the-counter (OTC) medicines, biologics, medical devices, combination products (e.g., nasal spray), cosmetics, and foods. *MedWatch* volunteers are prompted to fill out either a 3500 or 3500B form depending on the individual's role as a health professional or consumer/patient. Once the appropriate form is selected, the system generates a report ID. The system records the report date, demographic information, and description of the potential risk before allowing the reporter to submit the form to the FDA electronically. Using this information, the FDA can identify threats and, when needed, issue safety alerts informed from this tool. *MedWatch* can be easily accessed at

https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home. Supplementary to encouraging patient participation, the FDA also provides educational tools to lower consumer risk.

The FDA provides several educational campaigns to lower consumer risk. For example, the BeSafeRx campaign raises awareness about the dangers of buying prescription medicines from fake online pharmacies (FDA, 2015). BeSafeRx provides tips on identifying safe online pharmacies, such as ensuring the pharmacy is licensed within the patient's state's board of pharmacy. To supplement this, the FDA provides a database in which this information can be received quickly. The database can be explored at: https://www.fda.gov/drugs/besaferx-know-your-online-pharmacy/know-your-online-pharmacy.

The FDA does not limit developing educational campaigns and tools to consumers. Manufacturers and other supply chain personnel can also find aid through tools such as the supply chain security tool kit. Developed through a collaboration with the Asia Pacific Economic Cooperation, the FDA created the supply chain security tool kit focusing on medical products (FDA, 2017b). Constructed to improve supply chain security, the tool kit addresses vulnerabilities in the medical product supply chain. It provides recommendations on best practices to prevent and detect substandard medical products before reaching consumers (FDA, 2017b). The educational tool kit was developed to provide training material to educate its readers on the supply chain by covering ten categories:

- good manufacturing practices
- good distribution practices
- good import/export practices

- clinical/retail pharmacy practices
- product security
- detection technology
- internet sales
- track and trace systems
- surveillance and monitoring
- single points of contact

The full tool kit can be accessed at:

http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChainToolkit_170317.pdf.

2.5 Conclusion

Pharmaceutical manufacturers execute quality control and other good practices to provide safe high-quality drugs. The FDA is tasked with ensuring manufacturers are performing such procedures. Faced with limited resources, the FDA has developed novel tools to aid supply chain oversight, including a risk-based approach to prioritizing on-site inspections in addition to analytical testing of drugs in FDA laboratories. However, arguably two of the largest recalls in recent years were initiated by Valisure, not the FDA. The success of Valisure has since inspired other quality testing pharmacies such as the UK Central Pharmacy to emerge. Lastly, the FDA provides tools to encourage participation and education of quality manufacturing for both patients and supply chain personnel.

CHAPTER 3. GAMING AND BASIC THEORY

3.1 Introduction

The drug development process (DDP) is both lengthy and expensive, consisting of five key stages: drug discovery and development, preclinical, clinical, Federal Food and Drug Administration (FDA) review, and, lastly, post-marketing surveillance (see Figure 3.1). Stage 1-drug discovery and development consists of efforts in identifying a key disease target such that the design of, or repurposing of, a compound can be developed to stop or reverse the effects of a disease. Once a lead compound is identified, development occurs such that preclinical trials may be conducted. During the development stage, information on the lead compound is gathered, such as absorption, distribution, metabolizing, excreting, and toxicity data, among other information. The preclinical stage moves the compound into in-vivo and in-vitro testing. The studies conducted within this stage, though not very large, provide critical information that details the compounds dosing and toxicity levels before moving to the next stage. Preclinical studies aim to answer basic drug safety questions but neglect gathering information on how the drug interacts with the human body. This information is gathered in clinical trials.

Clinical trials are the third and arguably most critical stage of the DDP. The clinical stage consists of 3 key phases starting with phase 1. Phase 1 consists of approximately 20-100 human subjects with the disease or conditions the active pharmaceutical ingredient (API) is designed to address. The purpose of this stage is to screen for safety and dosage. Phase 1 requires several months and functions as a gateway to phase 2 with a passage rate of approximately 70% of drugs in phase 1 entering phase 2. (FDA, 2018a). Once a drug candidate reaches phase 2, the number of human subjects participating in the study goes

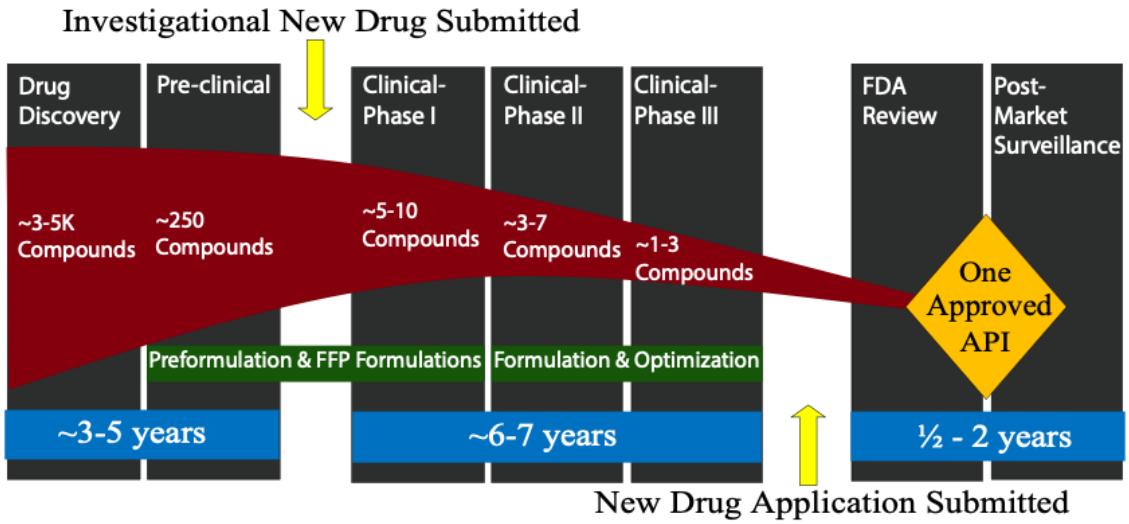

Figure 3.1 Graphical summary of the drug development process. Diagram has been modified and expanded from (Marsac, 2019). Where API stands for active pharmaceutical ingredient and FFP is fit-for-purpose. More on the FFP approach within the early drug formulation stages can be found in (Qiu et al., 2017).

up to several hundred, all of whom are diagnosed with the disease or condition the API is designed to treat. Within this phase, efficacy and side effects are screened. This process can last for several months up to two years. About 33% of drug candidates that enter this stage move into to phase 3. Phase 3 extends the study to at least 300 human subjects but can reach 3,000 (FDA, 2018a). All subjects studied in this phase also have the disease or condition the API is designed to address. This phase is one of the longest-lasting, between 1-4 years. The purpose of this phase is to further screen efficacy and adverse events. Approximately 25% of drug candidates move on to phase 4, in which several thousand human subjects are screened (FDA, 2018b). This phase provides a final gateway to approval through screening safety and efficacy. Lastly, the drug candidate must be approved through regulatory agencies.

Once a drug candidate has sufficient evidence of safety and effectiveness for its intended use (provided by the preclinical and clinical phase results), the drug developers may file a new drug application (NDA). Filing the NDA signals the intent to market a drug and should be submitted to the FDA for approval in the United States.

The application should include all preclinical data, clinical data, and information concerning product labeling, directions for use, patent information, drug abuse data, and more. After review, if the drug candidate is considered safe, this stage of the DDP will refine drug labeling before the product launch (FDA, 2018b). Once a drug product is launched, stage 5 provides product safety surveillance for the drug's life cycle. This stage includes inspections of manufacturing sites, oversight of drug advertisements, adverse event recording, and more (Campbell et al., 2020b; FDA, 2018c). Indeed, the DDP is a streamlined approach to drug development. However, the process has faced criticism.

Despite having general improvement and success over time, the DDP has often been criticized as a risky, slow, and expensive process (Djulbegovic et al., 2014; Kaitin, 2010; Kaitin and Dimasi, 2000; Mattina et al., 2017). Risky because the DDP involves exposing hundreds to thousands of human subjects to a drug candidate estimated to have about a 1 in 5 to 1 in 10 chance of being deemed safe to market (MIT, 2018; Seaton, 2011). In addition, the process is financially risky for the drug developer with estimates of the clinical-stage alone, costing upwards of $19 million (April, 2018), and the entire DDP estimated between $2-3 billion (DiMasi et al., 2016, 2003). Clearly, there is a need to cut costs. However, cutting costs within the DDP is challenging due to rigorous guidelines and standards that must be met. Despite the difficulty of changing the process, computational advances have streamlined decision-making (Sale, 2001).

Computational methods are now widely used throughout the DDP to yield better-informed decisions. Indeed, such methods have the potential of saving millions within the DDP (Kumar et al., 2006). For example, pharmacokinetic (PK) modeling can save resources and expedite the DDP by reliably predicting in-vivo Absorption, Distribution, Metabolism, and Excretion (ADME) properties of a drug (Gallo, 2010). PK and pharmacodynamic (PD) modeling are well established in the realm of pharmaceutical development and, for this reason, will not be mentioned further in this chapter. For interested readers, the authors suggest (Andes and Craig, 2002; Barber and Bourne, 1971; De La Torre et al., 2000; Javaid et al., 1983; Meredith, 2003; Urso et al., 2002). Instead, this Chapter will focus on emerging computational strategies for problem-solving in the pharmaceutical industry.

This Chapter will first review simulations, and emulations as they are used in the DDP. Topics such as molecular modeling will be discussed including methods such as the Grand Canonical Monte Carlo and Grand Canonical Alchemical Perturbation. Further advances in macromolecules modeling alongside the trending biologics market is discussed. Artificial intelligence (AI) techniques will also be discussed. After this a short introduction to game theory and gaming terminology is presented before introducing applications of game theory modeling in drug development.

3.2 Simulations, Emulations and Predictive Modeling throughout the Drug Development Process

Computational studies are now a vital part of the DDP. Indeed, computers have allowed for rapid access to data and turnaround of analyses. Further, investigation of processes far too complex or resource-draining to be studied experimentally are now

possible through computation investigations (Aminpour et al., 2019). For example, molecular docking a molecular modeling (MM) technique used to predict preferred molecular orientation is now readily conducted (Case, 2000; Dar and Mir, 2017). Other MM methods are useful in drug discovery and will be discussed in more detail below.

3.2.1 Drug Discovery

MM and similar computational chemistry models have become deeply woven into the drug discovery process. Applications in drug discovery range from predicting the effect of ligand-mediated water displacement using the Grand Canonical Monte Carlo (Bodnarchuk et al., 2020) to modeling molecular mechanics with Poisson– Boltzmann Surface Area (MM/PBSA). Further MM is often used for identifying both potential ligands and their binding site(s) on drug targets (Borhani and Shaw, 2012). Promising examples of this type of work can be found in (Borhani and Shaw, 2012; Wang et al., 2001; Wlodawer, 2002). However, MM still needs further development. For example, despite high throughput and industrial attention, MM/PBSA, accuracies are still low. Typical correlations between predicted and experimental binding free energy values fall between R squared values of 0.52 to 0.69. (Borhani and Shaw, 2012; Brown and Muchmore, 2009). Though it should be noted variants of MM/PBSA have been shown to improve these correlations slightly they are still low (Brown and Muchmore, 2009). Expanding on this - free energy calculations (like those used in MM/PBSA) can be categorized as alchemical free energy and conformational free energy calculations (Meng et al., 2011). Alchemical free energy methods such as free energy perturbation, and thermodynamic integration are considered some of the most promising methods for improving overall model accuracy (Brown and Muchmore, 2009; Michel and Essex, 2010; Woo and Roux, 2005). One

advantage with alchemical free energy methods is their ability to account for solute-solvent interactions while allowing for changes in environmental conditions such as pH and temperature (Gapsys et al., 2016; Kilburg and Gallicchio, 2018). Indeed, the Grand Canonical Alchemical Perturbation is now used alongside the Grand Canonical Monte Carlo as it is well suited for modeling occluded binding sites where solvent exchange with bulk is important (Bodnarchuk et al., 2020; Bruce Macdonald et al., 2018). Additionally, alchemical free energy methods have even outperformed Rosetta protocols in capturing trends in the ionizing mutations of the bacterial protein, Barnase (Gapsys et al., 2016). Suggesting that despite some drawbacks, MM will be a key tool for studying, designing, and developing new drug candidates moving forward.

Over the last several decades, biologics have emerged as the next generation of therapies providing blockbuster treatments such as Humira and Insulin (Eichman, 2018; Valeur et al., 2019). Biologics, sometimes referred to as biopharmaceuticals, consist of bioengineered macromolecular products such as proteins- and nucleic acid-based drugs (Ronald, 2008). This trend is followed alongside significant efforts in computational modeling of macromolecules for drug design, such as the effort in developing anti-HIV drugs conducted by Jorgensen's group (Jorgensen, 2016; Smith et al., 2006). The progress made within the past few years has enabled the prediction and design of macromolecular structures at near-atomic accuracy (Das and Baker, 2008; Kuhlman et al., 2003). Indeed, such efforts have allowed for both computational chemistry and biology software programs to emerge. One of the most notable of these programs being the Rosetta software suite first developed by Baker's group (Das and Baker, 2008; Editors, 2020). The Rosetta software aids researchers in understanding macromolecular interactions such as protein interaction

with drug compounds (Baynham et al., 2018). Further, Rosetta's de novo method has been used to inform the development of vaccines (Correia et al., 2014; He and Zhu, 2015). Rosetta also provides other ways to aid drug discovery by allowing calculations of energy functions and searching conformations. For more on Rosetta see (Alford et al., 2017; Das and Baker, 2008; Editors, 2020; Park et al., 2016). Another notable computational method applied to drug discovery and design is AI.

The late Dr. Patrick Winston defined AI as the study of the computations that make it possible to perceive, reason, and act (Winston, 1992). In essence, AI is attempting to make machines mimic cognitive functions, including decision-making. The subset of AI most relevant to drug discovery, and arguably the DDP as a whole, is machine learning (ML). ML is a technique that utilizes statistical methods with the ability to learn from past data sets to detect patterns or regularities (El Naqa and Murphy, 2015). When the assumption that the near future will not be too different from the close past, holds, then this technique can make accurate predictions about the future. Making it a good fit for modeling drug compounds' physical and biological properties (Brown et al., 2020; Cherkasov et al., 2014). A further subfield of ML is deep learning (DL), which has seen a resurgence recently due to advances in big data and computing capabilities to support the method (see Figure 3.2 adapted from (Zhu, 2020)).

DL utilizes artificial neural networks with representation learning that adapts and learns from a large training set of data to fuel its predictive power (Lecun et al., 2015) . Since DL's resurgence, it has been used in multiple drug discovery works, with one of the most notable being Méndez-Lucio's de novo generative model that can automatically

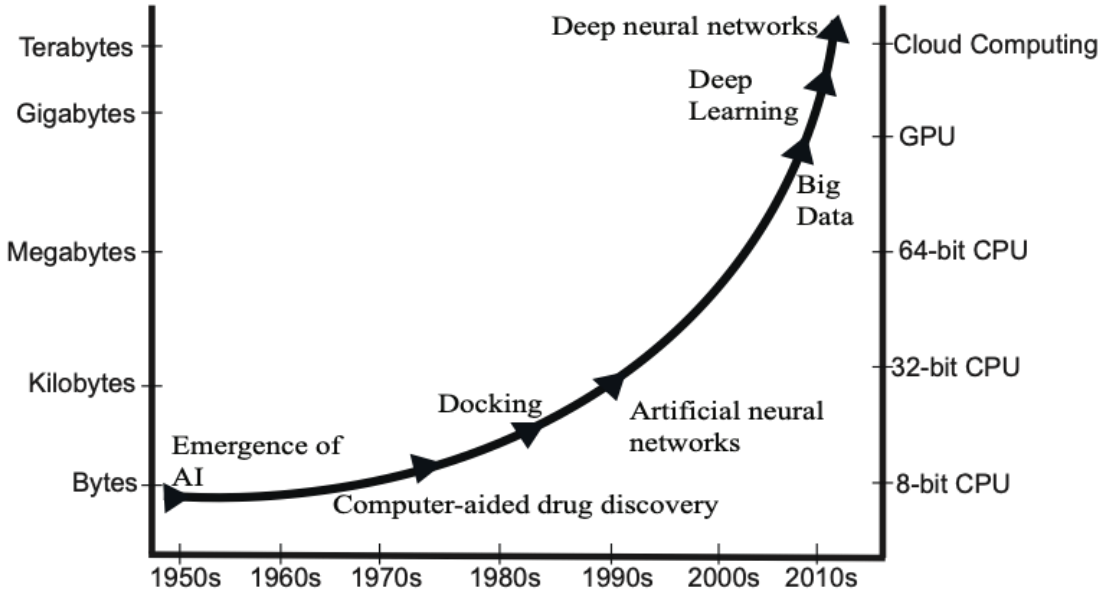

Figure 3.2 Graphical summary of the historical progress of artificial intelligence in drug discovery as a function of increasing data size and processor improvement. Consists of information from (Zhu, 2020).

design molecules so long as the gene expression signature is provided (Méndez-lucio et al., 2020) . On the other hand, AI techniques are also helping repurpose drugs.

Zidovudine, Atomoxetine, Rituximab, and Rituximab are just a few of many drug compounds that have been successfully repurposed (Pushpakom et al., 2018). In essence, drug repurposing is an industry movement to develop marketed drugs for other diseases; they were not originally marketed to treat. It is an approach that aims to lower risks (e.g., unexpected adverse events) and development costs associated with the DDP (Brinkman et al., 2020; Pushpakom et al., 2018). AI has proved helpful in drug repurposing, allowing for the screening of thousands of drugs to treat a target disease in a short amount of time. For this reason, it was employed to identify existing drugs for the treatment of COVID-19

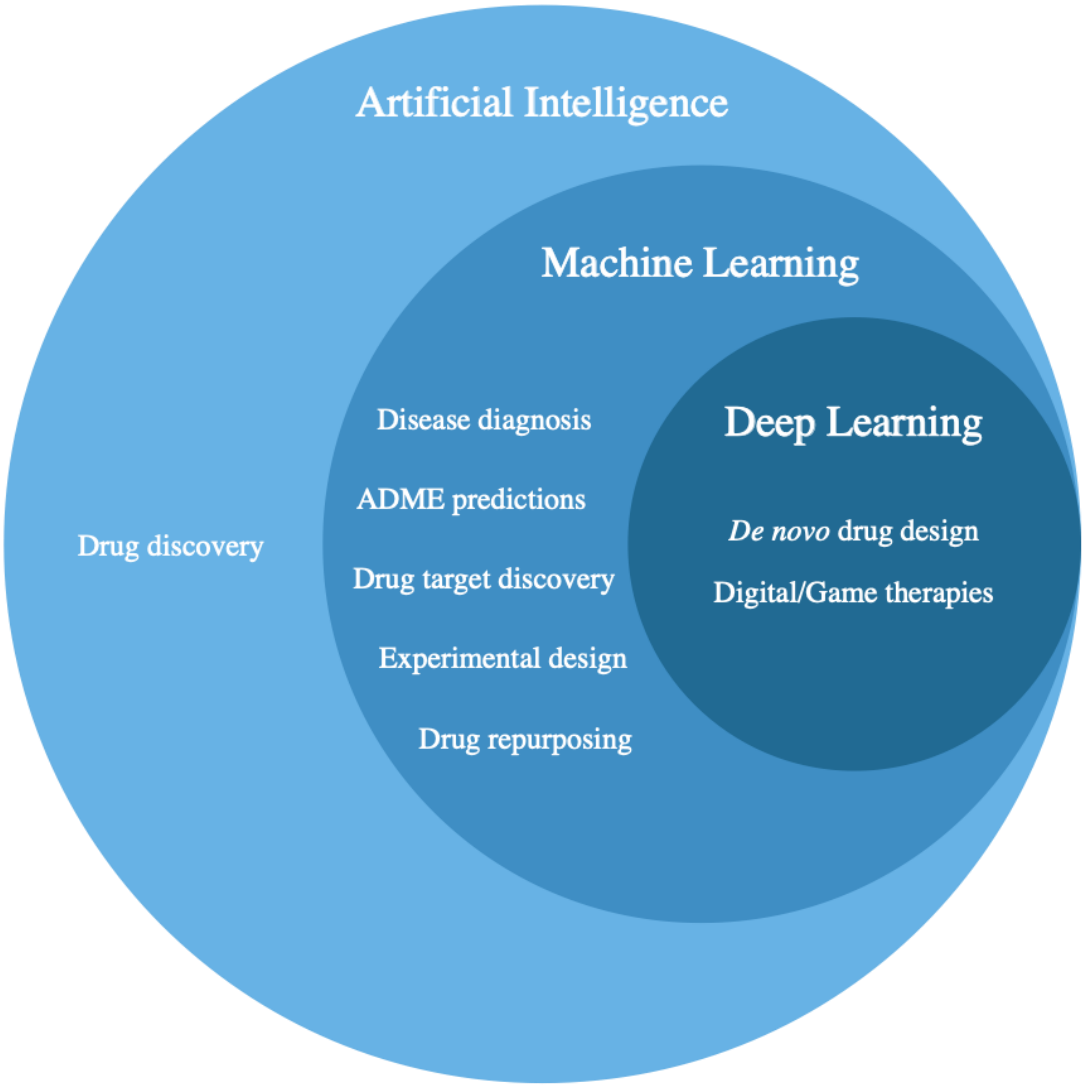

Figure 3.3 Graphical summary of artificial intelligence (AI) and its subfields: machine learning and deep learning, in drug development. Consists of information from (Lodder and Tiitto, 2017; Mak and Pichika, 2019).

(Gordon et al., 2020; Ke et al., 2020; Olena, 2020). For more on AI's role in drug discovery, repurposing, and design, the authors suggest the following articles (Aliper et al., 2016; Brown et al., 2020; Hessler and Baringhaus, 2018; Mak and Pichika, 2019; Michie, 1968; Pushpakom et al., 2018; Yang et al., 2019; Zhavoronkov et al., 2020; Zhu, 2020). Further, AI's utility in the DDP extends beyond the drug discovery stage (see Figure 3.3) (J. Chen et al., 2018) and this will be discussed in the next section.

3.2.2 Pre-clinical

A lead compound is moved into in-vivo and in-vitro testing during the preclinical stage to begin investigating the compound's safety. Further characterizing of the compound's physicochemical properties, which is often referred to as pre-formulation, takes place. The pre-formulation stage is used to inform the formulation process throughout development. Formulation is critical as functional excipients have been shown to stabilize otherwise non-stable compounds and provide adequate bioavailability to otherwise non-orally bioavailable compounds (Arce et al., 2020; Liechty, 2010; Williams et al., 2013). Making pre-formulation vital to the drug candidate's potential success. Like other stages, AI techniques have begun informing the pre-formulation process. For example, Ebube's artificial neural network (ANN) for the characterization of physicochemical properties of amorphous polymers. In this study the ANN was trained on experimental data of polymer properties, including water-uptake profiles, glass transition temperatures, and viscosity values. The software was then tested and found to have a low percent error when making property value predictions on different amorphous polymers and their physical blends (Ebube et al., 2000). Other techniques, such as population data-driven models, have been developed to inform early-stage excipient choice. Campbell and Lodder's population data-

driven model mines databases for intake and shipping amounts on cyclodextrin (BCD) as a food additive. By utilizing this data, predictions of daily exposure to the population are made such that formulation amounts may be kept below that level. Allowing formulators to avoid adding significantly to BCD exposure of human subjects. Thereby, obviating the need for extensive preclinical formulation and toxicology studies- speeding a lead compound to the clinic and cutting development costs (Campbell et al., 2020b; Lodder, 2017).

3.2.3 Clinical

3.2.3.1 The Clinic

The clinical stage of the DDP consists of multiple phases and subphases. Starting with phase 1, a small subsample of the population is exposed to the candidate compound. Involving potential health risks and misconceptions for the patients while providing high financial risk for the sponsoring company (April, 2018; Kaitin, 2010; Pentz et al., 2012). For these reasons, care must be taken in the planning and development of phase 1 studies. The studies must provide accurate and rapid information, such as maximum tolerated dose (MTD). Phase 1 designs can be categorized into two main groups based on the algorithms used: rule-based designs (such as the commonly used 3 + 3 design) and model-based designs (e.g., the continual reassessment method (CRM)). These algorithms, at their core, use statistics to design trails that minimize the number of patients receiving sub-therapeutic or toxic doses and maximize the number of patients treated at therapeutic dosing range (Lin and Shih, 2001; Wong et al., 2016). Although model-based designs such as CRM have proven to be more accurate and efficient when optimizing for MTD, they cannot compare to the practicality and simplicity of rule-based algorithms. For this reason, the rule-based

3+3 design has been used in at least 80% of phase 1 trials (Z. Chen et al., 2018). With extensive use of the 3+3 design, researchers have developed tools to facilitate its use, such as Chen's interactive calculator for operating characteristics of phase 1. Here Chen and colleagues developed a stand-alone interactive software for convenient calculations of these critical operating characteristics. Using this software allows users to avoid the complex formulas and need for extensive statistical knowledge- making the 3+3 design even easier to use (Z. Chen et al., 2018). Variants of the 3+3 design have been developed for more complex investigations, such as the 3+3+3 design proposed by Braun and Alonzo to extend the concepts of 3+3 to two-drug combination therapies (Braun and Alonzo, 2011). Similar design models have been developed for phases 2 and 3. Typically these models aim to reduce sample size while still gathering the necessary information (Khan et al., 2012). AI is also beginning to emerge as a technique to make clinical trial designs more efficient (Harrer et al., 2019). MIT researchers have described novel and non-trivial reward functions for self-learning reinforcement learning (RL) algorithms for dose de-escalation studies during clinical trials to alleviate chemotherapy toxicity (Shah, 2020; Yauney and Shah, 2018). For more on this, the authors recommend the following articles (Ho, 2020; Peck et al., 2020; Shah, 2020).

3.2.3.2 Drug Processing, Manufacturing, and Storage

During the DDP's clinical stage, the drug will undergo stringent development "behind the scenes" to ensure the drug will be practical and safe to market. This consists of developments regarding drug processability, scale-up, formulation, and storage stability. Information relating to the drug's stability over time, how the drug will be stored, and how it will be formulated are critical in gaining FDA approval. Without optimizing each of these

elements, the compound can be rendered useless and fail to gain FDA approval. Computational techniques based on fundamental engineering principles such as thermodynamics and fluid mechanics are often used throughout these developments. The knowledge gained through these techniques directly feeds information that influences decision-making on scale-up and machine parameters. One commonly employed technique is computational fluid dynamic (CFD) modeling, which is often used for the optimization and scale-up of unit operations such as fluidized beds, pan coaters, hot melt extruders, and spray-dryers (Hyvärinen et al., 2020; Ketterhagen et al., 2019; Poozesh and Bilgili, 2019; Sarkar et al., 2019). Combining CFD with other numerical modeling has allowed for a more holistic investigation of processing and manufacturing than could be done with experimental methods alone (Pandey et al., 2017). For instance, spray-drying is complex in terms of machine parameter interactions, making it difficult to experimentally isolate any one variable. However, utilizing CFD and numerical methods has given insight into droplet atomization, droplet drying kinetics, and the droplet formation process (Mezhericher et al., 2009; Poozesh et al., 2020, 2018). Such information aids in developing a successful manufacturing process and the scale-up of said process. These aspects are critical to the DDP as it would be devastating to a candidate compound that is deemed safe and efficacious, but unable to be produced on a mass scale such that patients may benefit. Furthermore, advances in CFD occur at a rapid pace, and a notable method that is beginning to emerge is the use of CFD emulators.

Emulators are a statistical model of a simulated model estimated from the simulation's observed input-output (Grow and Hilton, 2018). In essence, once established, emulators can replace the simulation, which can dramatically cut down the computational cost with the potential of simplifying the modeling. Aspects that would be useful in CFD simulations of pharmaceutical unit operations as these models can become extremely complex, computationally costly, and time-consuming to run (Moonen and Allegrini, 2015). Although not prevalent in pharmaceutical literature when writing this chapter, the

authors suspect a growing interest to occur over the next several decades as other industries such as environmental engineering further utilize and advance the technique (Albert, 2020).

Computational methods useful in informing decisions in formulation and stability will generally be models of solid-state materials or solid-liquid interactions. The modeling of polymer-solvent diffusion with Monte-Carlo simulations is one example (Gartner and Jayaraman, 2019). Such a simulation is critical to formulation and stability as even a 1% water content has shown to induce phase separation in amorphous solid dispersions, thereby decreasing the stability of the drug formulation as a whole (Mugheirbi et al., 2017). Nevertheless, Gartner and Jayarman's simulation, alongside similar simulations, could decrease the time and costs currently being used on studying environmental effects on drug formulations. Another example is Schwartz's optimization of formulation via computer analysis (Schwartz et al., 1973). Other methods of solid-state modeling include ML techniques and for a review of these topics see (Schmidt et al., 2019).

3.2.3.3 FDA Review and Post-marketing Surveillance

FDA's new drug application (NDA) review process consists of 6 steps. I) First, the drug sponsor and FDA will host a review meeting before the NDA is filed. Assuming all goes well within this meeting II), the drug sponsor will then be responsible for formally asking the FDA to approve their drug by electronically submitting a completed NDA. The NDA will include all animal and human data, the analyses of the data, data regarding the drug's behavior in the body, and how it is manufactured, which includes formulation. III) Upon submitting the NDA, the FDA has a 60-day window to decide whether the application should be filed for review. IV) Assuming the NDA is filed, the review process will then take place. Evaluation of the drug's safety and effectiveness will be of top concern. If declared safe and effective, the FDA will then move into V) developing the drug labeling with the drug sponsor before VI) inspecting the manufacturing site that the drug product

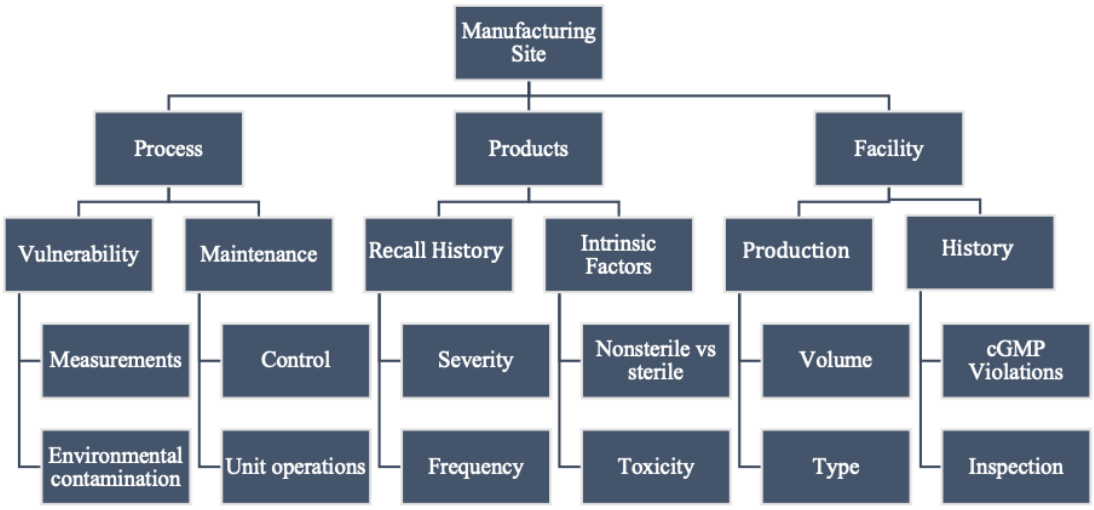

Figure 3.4 Representative of FDA's site selection tool hierarchy. Conceptually, the tool deconstructs the manufacturing site into three components: process, products, and facility. These components can be thought to summarize the various risk factors of t the site. These risk factors are then weighted and mathematically combined to output a site risk score in which the manufacturing site is listed for inspection.

will be produced. Although humans stay at the heart of decision-making within this stage, computers are still utilized throughout the process for data transfer and communication. Computers play a more central role in post-market surveillance. For example, FDA's computerized MedWatch system allows for easy reporting and storing of adverse event data. Internal utilization of computer power has emerged within the FDA, such as the FDA's site selection model used to prioritize on-site inspections. An outcome of the Pharmaceutical Quality for the 21st Century — A Risk-Based Approach initiative, the model ranks manufacturing sites by a numerical score (Campbell and Lodder, 2021b;

CDER, 2018). The score reflects the manufacturing site's probability of failing cGMP. The model works through analyzing top-level components while considering the possible risk factors to produce the manufacturer's score (see Figure 3.4). For more details on the FDA's site selection tool, see (Campbell and Lodder, 2021b; FDA, 2004a).

Next, we will begin our discussion of gaming as a novel tool to solve pharmaceutical problems. The following several sections are intended to provide the reader with fundamental knowledge of game theory and gaming in a scientific context. For those already familiar with these concepts, these sections may be skipped over. The sections following these introductions will discuss gaming as a tool in which it relates to the field of pharmaceuticals and the DDP, such as its role in molecular problem-solving.

3.3 Basic Game Theory

This section begins by describing game theory and its methodologies in a traditional, behavioral, and algorithmic light before moving into essential elements of games and standard games.

3.3.1 Game Theory: Traditional, Behavioral and Algorithmic

The collective action problem, or sometimes referred to as the social dilemma, is described as a situation in which individuals would gain more by cooperating; however, they often fail to cooperate due to conflicting interests (Liebrand, 1983). The social dilemma concept is fundamental to game theory as it can be used as a model for many game interactions; such is the case for the famous Prisoner's dilemma game (Liebrand, 1983). Game theory is especially equipped to find optimal strategies for such dilemmas (Anderson et al., 2016). As it is known today, game theory was established by John Von

Neumann and Oskar Morgenstern in their publication Theory of Games and Economic Behavior. In this text, Neumann and Morgenstern showed that economic and social questions could be described in games of strategy (Anderson et al., 2016). Since then, games of strategy have been used to bring quantitative insights into war and economic decision-making. Neumann and Morgenstern's methods also became the standard in applying game theory.

Game theory methodology begins by establishing a game description. Then the goal is to identify stability in the game, with the standard approach being to assume the agents playing will adapt their decision-making to conform to a Nash equilibrium. Nash equilibria is a proposed solution to non-cooperative games in which, given one player's strategies, the other player has nothing to gain by changing their own. Nash equilibria and other refined solutions to games have been extensively studied and, therefore, will not be further defined in this chapter; however, the interested readers are pointed to the following sources for further information (Daskalakis et al., 2009; Munro, 1992; Nash, 1950; Sethi, 2008). The last step involved in game theory methodology is to translate the game's solution into practical terms.

Today, game theory is used in a wide range of industries outside of warfare and economics, including law and philosophy (Anderson et al., 2016). Mass amounts of work have shown that game theory can accurately predict behavior in many situations. Despite this, there are still situations in which traditional game theory fails to accurately capture human behavior (Goeree and Holt, 2001). For example, the Traveler's Dilemma is a game that experimentally converges or diverges Nash equilibrium depending on the bonus/malus parameters used (Capra et al., 1999). For this reason, subfields of game theory have

emerged, such as behavioral game theory (BGT), which has been used in neuroscience problem-solving (Camerer, 2009; Wright and Leyton-Brown, 2012). BGT is distinct compared to traditional game theory as it does not seek to pinpoint a correct strategy or action by mathematical models beforehand. Instead, BGT is driven by empirical data (e.g., experiments and observations) to develop a model. That is, BGT is fundamentally based on the concepts of traditional game theory (TGT), but methodology differs. In BGT, the methodology starts with a game or naturally occurring situation. Once a game is identified, it should be classified into a standard game such that TGT can provide predictions based on one or two fundamental game theory principles. Experimentation is then conducted, and if behavior differs from the predictions, formal game theory is extended to incorporate the proposed explanation for the inconsistency (Camerer, 1997). There are four prominent models used in BGT; Quantal Response Equilibrium, Level- k, Poisson–Cognitive Hierarchy, and Quantal Level-k (Wright and Leyton-Brown, 2010). Although out of the scope of this chapter, formal definitions of each model can be found elsewhere (McKelvey and Palfrey, 1995; Wright and Leyton-Brown, 2012). Another important subfield of game theory is algorithmic game theory or AGT.

AGT utilizes mechanism designs which ask the question- how does one design systems such that agents' selfish behavior results in desired community goals (Mavronicolas et al., 2007)? Mechanism designs are extended to algorithms in AGT and termed algorithmic mechanism designs (AMD). AMD considers computational tractability to concepts of mechanism design and focuses on optimization problems of complex networks such as the Internet (Mavronicolas et al., 2007). The Internet and similar complex networks are often made up of intelligent agents or software entities that carry out some

set of operations on behalf of a user or another program with some autonomy level. These agents must collaborate in actions in which they are involved; however, complex networks breed selfish natures, so the need for game-theoretical strategies emerges. Typically, non-cooperative games (see section Basic Elements and Types of Games) are used to provide solutions and insights into problems such as congestion, security, and routing. AGT has also been extended into scientific fields such as computational biology. For instance, Lamiable compared a novel game theory-based algorithm to a more traditional global optimization approach to predict conformations of large RNA molecules (Lamiable et al., 2013). By taking advantage of RNA's hierarchical structuring, with a secondary structure-forming first and a tertiary structure following, the researchers were able to decompose molecules into helices and junctions- located between said helices. From here, an initial secondary structure is formed that lacks any tertiary structuring. This initial confirmation represents a shaping in which nodes are locally stabilized but neglects the possibility of more long-distance interactions. To implement tertiary structuring and hence the possibility for long-range interactions the researchers used a game theory-based algorithm that took a local egoistical approach. The algorithm allowed each node to maximize its own payoff function while also considering the forces applied to each node. The results of this study showed that the game-based algorithm provided a more authentic prediction of tertiary links between architectural elements of the RNA molecules. For more on AGT, see (Elkind and Leyton-Brown, 2010; Roughgarden, 2008).

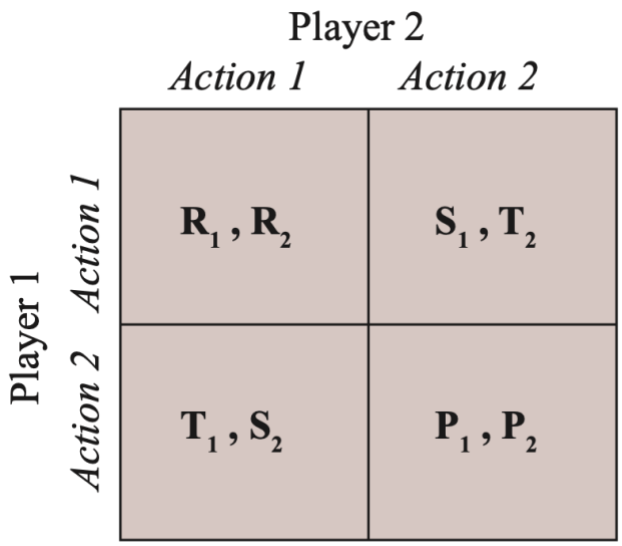

Figure 3.5 Generic two-player simultaneous, game matrix with payoffs R, T, P, and S. Where the subscripts indicate players 1 or 2, respectively. The payoff is an ordinal utility number assigned to a player at the outcome.

3.3.2 Basic Game Elements and Types of Games

As the field of game theory has developed, distinct terminology and classification systems have emerged. This section will provide a brief overview of common terminology used and how games are classified.

Classifying games:

Zero-sum and non-zero-sum games: In zero-sum games, the payoff of all players add to equal zero. That is points earned by one player come at the loss of points from another player. Non-zero-sum games, the payoff of players does not equal zero. Therefore, in non-zero-sum games, one player's benefit does not necessarily come at the loss of another.

Cooperative and Non-Cooperative games: In Cooperative games, players are allowed to communicate between themselves. This opens the door for players to corporate, and for actions to emerge that are beneficial for the whole. In non-cooperative games, players are not given the privilege of communication.

Perfect and imperfectly informed games: In perfectly informed games, players are aware of the other players' past actions. This is the opposite of imperfectly informed games where at least one player is unaware of other players' previous actions.

Static and Dynamic games: Dynamic games require players to take turns to act. Static or simultaneous games, each player must act without knowing the action taken by the other players. That is dynamic games; players act one after another while static game players act simultaneously.

One-shot and Repeated games: One-shot games are games in which the players play the game once and for all. Repeated games are played in iteration. Repeated games allow for modeling the psychological side of a continuous relationship, including the concepts of reputation, threats, and promises.

Normal-form and Extensive-form games: Normal- or strategic-form games can be described by matrices (see Figure 3.5), whereas extensive form games are described by game trees (See Figure 3.6) (Ilhan and Anderson, 2016). For a further description of the difference between normal- and extensive-form games, see Figure 3.7 in the Standard Games section.

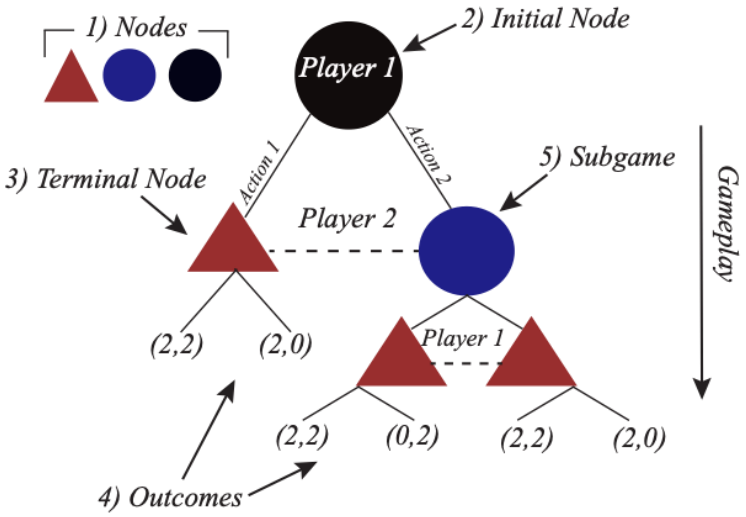

Figure 3.6 Generic game tree where 1) Node is a point at which a player chooses an action. 2) Initial node is the point at which the first action in the game occurs. 3) Terminal node: any node which, if reached, ends the game. Each terminal node corresponds to an 4) outcome. 5) Subgame: any connected set of nodes and branches descending uniquely from one node. Arbitrary payoff values are presented in parenthesis with the first coordinate corresponding to player 1's reward and the second coordinate corresponding to player 2's reward for any given outcome. Note that extensive-form games reach equilibrium differently than normal-form games (Munro, 1992).

Beyond terminology, understanding the general structure and basic elements of a game, allows players to decide how to play the game. Game strategies are defined as a program, instructing a player which action to take at every node (where player decision-making must occur- see Figure 3.6). Strategies can be pure, mixed, or hybrid approaches. Pure strategies players take the same action repeatedly. On the other hand, players can play a mixed strategy in which the action chosen is done according to a probability distribution over all possible actions. Next, standard games will be presented.

3.3.3 Standard Games

As mentioned, the concept of social dilemma is fundamental to many game models such as stag hunt (SH), the prisoner's dilemma, the bargaining problem, the snowdrift game, the unscrupulous diner's dilemma, and the centipede game (Mckelvey et al., 1992; Nash Jr., 1950; Sui et al., 2015; Teng et al., 2013). Additionally, the volunteer's dilemma and tragedy of the commons are used to study varying conditions of social dilemmas (Diekmann, 1985; Hardin, 1968). One of the most fundamental of these games is the SH. This game differs from its more famous counterpart, the Prisoner's dilemma, as it holds two pure-strategy Nash equilibria compared to one. This added degree of complexity allows SH to have a substantial relationship to the Prisoner's dilemma allowing circumstances that have been described as a Prisoner's dilemma to also be interpreted as a SH (Fang et al., 2002). For example, climate change contracts are often debated as to whether they are a prisoner's dilemma or SH, given varying assumptions (II, 2016; Szathmáry and Smith, 1995). SH began as a story by philosopher Jean Jacques Rousseau in his Discourse on Inequality (Skyrms and Irvine, 2001). Rousseau describes a situation in which hunters can remain faithful to their post such that the hunters may receive a stag. With the hunters having the inability to take down a stag alone, it is vital to remain faithful. However, given the opportunity to take down a hare on one's own, Rousseau sees that one cannot doubt a hunter would go off in pursuit of the hare in spite of it being less desirable (Rousseau, 1761). The discourse left many questions concerning the social contract and was eventually turned into the SH game (see Figure 3.7a). The traditional SH game (see Figure 3.7a) is described similarly to Rousseau's story by imagining two hunters that must

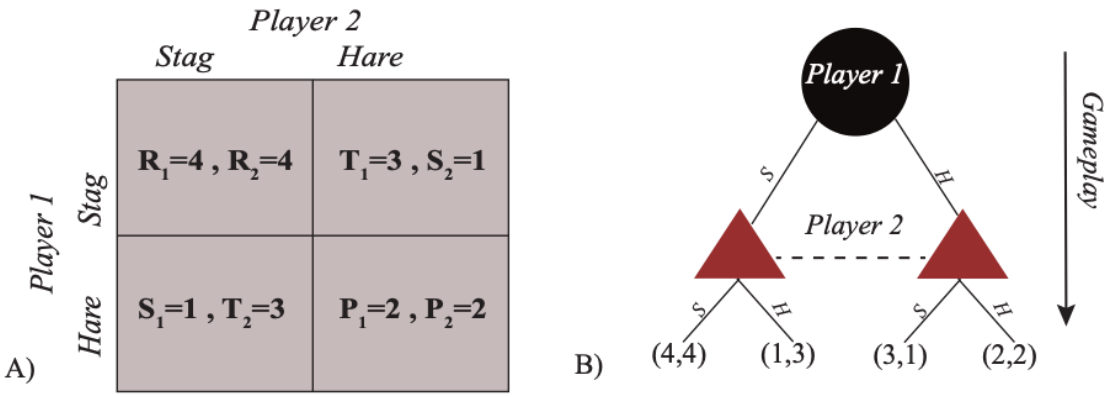

Figure 3.7 Stag hunt game descriptions A) normal-form simultaneously played B) extensive-form sequentially played with payoffs of $R > T > P > S$. Where $R = 4, T = 3, P = 2, and\ s = 1$.

choose independently (simultaneously played) to hunt a stag or hare. If both players cooperate and choose to hunt a stag, both do well and get the cooperating reward R. If one player cooperates, that is deciding to hunt a stag- but the other defects-that is deciding to hunt a hare-, the non-cooperative player gets the temptation reward T (the hare). In contrast, the cooperating player goes home hungry with nothing receiving the sucker's payoff S.

Traditionally, the SH is played simultaneously with a payoff structure of $R > T > P > S$. Alternatives of SH may be played sequentially, as depicted in Figure 7b. SH can also be generalized into N-player form as described by (Pacheco et al., 2009). Where it is generally agreed that cooperation becomes more difficult as N (number of players) becomes larger due to the problem of trust multiplying (Pacheco et al., 2009)..

3.4 Game Theory in Pharmaceutical Development

Nash equilibrium assumes that beliefs are consistent with actual decisions. However, beliefs are not likely to be confirmed out of equilibrium, and in such cases, learning will occur. Since this discovery, a large body of work has incorporated learning into models of

adjustment in games. For example, RL is often deployed for these tasks (Erev and Roth, 1998). On the other hand, game theory is often utilized in AI when multiple agents are solving logical problems. Indeed, game theory is often used in multi-agent AI systems, Imitation and Reinforcement Learning, and Adversary training in Generative Adversarial Networks (GANs). In addition, one of the oldest AI algorithms -MiniMax algorithm originates from game theory. Beyond supplementing network AI systems game theory has found utility in other areas of science and technology.

Game theory has influenced areas of science, including pharmaceuticals. Indeed, many AI-based examples described in the section Simulations, Emulations, and Predictive Modeling throughout the DDP were possible due to game theory. Yet, there are more examples such as, game theory-driven dosing regimens (Chmielecki et al., 2011; Enriquez-Navas et al., 2016).

Yauney and Shah game theory-driven dosing regimens explored reward incentives for their chemotherapy selecting algorithm as a function of reducing mean tumor diameter (MTD) (Yauney and Shah, 2018). Here the game was between the RL agent and the tumor. The agent was given a choice to dose Temozolomide (TMZ) or procarbazine, lomustine, and vincristine (PCV) chemotherapies with different dosing options depending on the therapy chosen. These choices functioned as the agents' action set within the game. Various penalties and rewards for the agent's actions were explored, with the base incentive being MTD reduction. This study found that the learned dosing and expert dosing regimen agreed well (Yauney and Shah, 2018). Others have used game theory to optimize pharmaceutical product flows by modeling interactions within the PSC (Nagurney et al., 2013). Using a basis in non-cooperating gaming, the model investigated interactions between

pharmaceutical firms and contractors in outsourcing activities such as selecting a contractor. Assumptions for these games included that the pharmaceutical firms are cost-minimizing, and the contractors are profit-maximizing. Nash-Bertrand equilibrium characterized the game, which fulfills variational inequality for both the firm and the contractors. Game theory has also been used to provide insights into the business of the pharmaceutical industry.

Game theory provides insights into pharmaceutical companies as commercial businesses. For example, the bargaining game has been used to model the interactions between regulators and pharmaceutical firms (Wright, 2004). In Wright's, work game theory was implemented to understand the interactions for price negotiations and regulations in Australia. A country alongside the Netherlands, New Zealand, and the United Kingdom which regulates pharmaceutical prices consumers pay. The theoretical game model investigated the implications of the Australian Pharmaceutical Benefits Scheme design. The results of this study suggested that although firms agreed on lower prices with regulators the firms receive higher payoffs than in unregulated systems.

3.5 Conclusion

Technological breakthroughs of the 20th and 21st centuries have provided significant advancements in computer sciences. Much of the computational advancement, especially in the realm of ML, has a basis in game theory. Allowing, innovative computational methods to solve complex problems. This chapter showed that despite challenges set forth by heavy regulation and strict guidelines innovative computational methods have improved problem-solving capabilities in the pharmaceutical industry. Complex processes that have otherwise been too time consuming and costly to study can now readily be modeled. Thereby, catapulting the industry into the 21st century of problem solving. Game theory

especially has allowed for innovative computational methods to emerge for solving pharmaceutical problems that traditional methods alone could not. This chatper has described the science of game theory and revealed its role in solving pharmaceutical problems.

CHAPTER 4. A NEW AGE OF PROBLEM SOLVING-SERIOUS GAMING FOR SCIENTIFIC SOLUTIONS

4.1 Introduction

Serious gaming or applied gaming are games not used solely for entertainment but alternative purposes, such as educating or solving scientific problems. Though the origins of serious games are in defense or militaristic applications, not scientific problem-solving. For example, America's Army, released in 2002, soon became a recruitment and even supplement rifle training tool for the military (Zyda, 2005). However, thoughts on games' relationship with human behavior date back beyond digital games to philosophers such as Plato of the 4th Century BCE (Wilkinson, 2016). During this time, Plato theorized that reinforcing certain behaviors in children's play would reinforce those behaviors as an adult (D'Angour, 2013; Wilkinson, 2016). Plato's thoughts began a debate on the purpose of play and games' applications, with most believing that play was only for children and absence of a meaningful purpose. It was not until Friedrich Schiller, and Jean-Jacques Rousseau introduced their ideas that play started to be considered a meaningful activity (Bentley, 2009; Wilkinson, 2016). Indeed, Rousseau's story of the hunters would later develop into SH, a standard game of game theory (Skyrms and Irvine, 2001). Although it took until the 18th Century to begin swaying the general opinions of play as an activity of purpose, it didn't stop some from at least metaphorically relating games to real-world problems. For example, in the 7th Century Chaturanga, an ancestor to Chess, is on record as being explicitly applied as a militaristic metaphor. Even its design seems to be of military origin (Smith, 2010; Wilkinson, 2016). Studies of strategic thinking games such as Chaturanga and Chess led to the development of Kriegspiel- a serious game similar to Chess that aimed

to simulate war (Favini, 2010). Kriegspiel was developed by the Prussian military and is thought to have been an essential instrument for the army. The game is also on record as being used by the Japanese navy in the Russo-Japanese war of 1904-1905 (Favini, 2010). Kriegspiel's success in gaming war led to creations such as the RAND Corporation by the US Air Force. Since RAND's inception, the corporation has developed games and models for world events such as the Cold War competition and nuclear warfare (Hournshell, 1997). In addition to the RAND Corporations' work on militaristic applications, work has also been conducted with medical applications, as demonstrated by the collaboration between RAND and the University of Pittsburgh School of Medicine (Mohan et al., 2018, 2014). In these studies, researchers used serious games to investigate cognitive loads' influence on physician decision-making by measuring trauma triage and transfer decisions. Splitting physicians into different load groups, the researchers found that those physicians who finished the study made decisions consistent with actual practice and that cognitive load could be manipulated in-game. Further, the results aligned with the cognitive theory predictions that state-when cognitive load increases, the use of heuristics increase (Mohan et al., 2014). Scaling this study to 320 physicians working at non-trauma centers in the United States, the researchers hoped to improve physicians' heuristics through game interventions. Although suffering data corruption, among other limitations, the work did suggest that the game interventions reduced under triage cases digitally compared to a text-based intervention that did not (Mohan et al., 2018).

This chapter will provide a comprehensive review of gaming as an innovative solution to pharmaceutical problems. Applications of serious gaming in the pharmaceutical industry will be discussed. Game-based therapeutics will be reviewed, including Akili's

groundbreaking EndeavorRX, the first FDA-approved game therapy for treating attention deficit hyperactivity disorder (ADHD) (Mueller, 2020a). Further, this article will summarize advances due to gaming in other industries and provide input on future gaming directions in pharmaceutical sciences.

4.2 Serious Gaming by Definition

In 2019 the FDA co-sponsored a free video game to prevent smoking entitled One Leaves, playable on Xbox and PC. The development came as a part of the FCB's "The Real Cost" campaign that promotes an anti-smoking agenda and highlights that out of every four teens who smoke cigarettes, only one will escape the addiction (Muoio, 2019). The statistic is provocatively played out within the game—allowing only one player of four to escape a horror-themed maze.

One Leaves' mission is to educate and scare its players from smoking cigarettes. Thereby, helping them avoid all the potential diseases that are linked to smoking. But serious gaming in health and pharmaceuticals, can be more than an educational tool. Indeed, serious gaming can be therapeutic as demonstrated by Akili's-EndeavorRx. After successful clinical trials, EndeavorRx became the first FDA-approved gaming therapeutic for the treatment of ADHD in 2020 (Kollins et al., 2020; Mueller, 2020b). EndeavorRx is intended for children ages 8-12 years old, with primarily inattentive or combined-type ADHD. Clinical trials showed that children within this age range had improved attention function after playing EndeavorRx. Where the computer-based Tests of Variables of Attention was used as the primary measurement tool (Pena, 2020). Unfortunately, the game did not come without side effects. Of those tested, 9.3% of the subject's experienced effects, such as frustration, headache, dizziness, emotional reaction, nausea, or aggression (Akili's Interactive, 2020a; Kollins et al., 2020). However, it is of the author's opinion that

these side effects are minimal compared to pharmacotherapy, as demonstrated in Table 4.1. Indeed, the most serve potential side-effects when treating with EndeavorRx is eye strain or joint pain. Compared to Adderall which may induce seizures. Furthermore, common medications used to treat ADHD are schedule II compounds- meaning; the compounds are controlled substances and have a high potential for abuse. An additional plus for EndeavorRx is comparable (though slightly higher) prescription pricing.

EndeavorRx prescriptions are for 96 days (about 3 months). Patients are to play uninterrupted for 25-30 minutes daily (Akili's Interactive, 2020a). For insured patients, the cost of this treatment is $450 (about $150 a month). Uninsured patients can get company assistance which lowers the cost to about $100 a month (Coey, 2021). Compared to pharmacotherapies such as Adderall XR which can run from $30-$70 for a 30-day supply* (Medical Security Card Company, 2021). Making a 96-day, Adderall XR prescription in the range of $96-$220 -a slightly cheaper option than EndeavorRx. However, as the company continues to grow, and the field of digital therapies matures these prices may decrease.

EndeavorRx is the first FDA-approved digital therapeutic of what seems to be many more to come given Akili's Interactive and their competitors continue to work on gaming treatments for other common disorders. Indeed, at the time of authoring this paper, Akili's Interactive is continuing pilot studies for three potential digital therapeutics AKL-T02, AKL-T03, and AKL-T04. Where AKL-T02 is a possible digital treatment for attention symptoms in children with autism spectrum disorder (Yerys et al., 2019). AKL-T03 and AKL-T04 are potential digital treatments of cognitive deficiencies in adults who suffer

*Estimate based on pharmacy pricing near Lexington, KY. Range representative of discount only rates not insurance rates.

from major depression (Akili's Interactive, 2020a). In addition, AKL-T03 is also undergoing feasibility studies as a potential treatment for cognitive impairment in patients with multiple sclerosis (Bove et al., 2019). Grendel Games, a Dutch serious gaming company, has not received FDA approval for their digital treatment Gryphon Rider. Regardless, the game was specifically designed to aid young children recovering from acquired brain injury (Grendel Game, 2014). Specifically, the game is designed to motivate children when repetitive rehabilitation exercises are needed. Children can play Gryphon Rider by moving their bodies as the game allows you to take the reins of a gryphon (or griffin)- a mythological creature with the body of a lion and head and wings of an eagle- and navigate various worlds. Further, game designers have also developed games for improved health.

Table 4.1 Side effects among common ADHD medications compared to that of EndeavorRX the digital gaming therapeutic.

Brand name	**EndeavorRX**	***Adderall**	***Vyvanse**	***Focalin XR**	**Strattera**
Generic name	None	Mixed amphetamine salt	Lisdexamfetamine	Extended-release dexmethylphenidate	Atomoxetine
Type	Digital therapeutic	Short-acting amphetamine stimulant	Long-acting amphetamine stimulant	Long-acting methylphenidate stimulants	Long-acting non-stimulant
Most common side effects among children and adolescents	Frustration, headache, dizziness, emotional reaction, nausea or aggression.	Loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever.	Anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.	Dyspepsia, decreased appetite, headache, and anxiety for pediatric patients and dry mouth, dyspepsia, headache, and anxiety.	Nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence
Additional side effects and cautions	Eye strain, joint pain	Seizures, eyesight change, blurred vision, serotonin syndrome, possible slowing of growth, agitation, hallucinations, coma or other changes in mental status, muscle	Rash, pyrexia, somnolence, hyperhidrosis, erectile dysfunction, decreased libido	Vomiting, gastrointestinal disorders, insomnia, libido changes	Irritability, anorexia, headache, dizziness, depression, insomnia, weight decrease.

		twitching, diarrhea.			

*Schedule II compound. The above table is not intended to be treated as all encompassing. Information for this table was found at (Akili's Interactive, 2020a, 2020b; American Academy of Pediatrics, 2019; Division of Teva Pharmaceuticals USA, 2017; Eli Lilly and Company, 2009; Kollins et al., 2020; Novartis Pharmaceuticals Corporation, 2017; Shire US Inc., 2015)

Dr. Jane McGonigal, a game designer who advocates for technology to channel positive attitudes and collaboration, developed the serious game SuperBetter. SuperBetter aims to improve mental health and resilience in its players, with promising results in randomized control studies (Roepke et al., 2015). Furthermore, SuperBetter has seen promising clinical trial results as a gaming intervention to reduce concussion symptoms in teenagers (Worthen-Chaudhari et al., 2017). Researchers have also gotten in on the fun of developing health-improving games.

Serious gaming therapies have also gained popularity among academic researchers such as Lodder and Titto's work through game repurposing the popular console and PC game-Minecraft (Lodder et al., 2017; Lodder and Tiitto, 2017). In these studies, Lodder's group developed specially designed training activities performed within Minecraft to determine if they affected executive function, working memory, or restraint in patients diagnosed with ADHD (Id et al., 2017). After a promising feasibility study, the digital treatment moved into clinical trials which at the time of writing is still in the recruitment phase (Lodder and Tiitto, 2017; Tiitto, 2019). Rehabilitation of the upper extremities for stroke patients through gaming is also being explored (Yates et al., 2016). In this review, Yates' claims that the literature seems promising for the use of virtual reality games as rehab therapies for stroke patients. Yates' found support that these gaming therapies can be

equivalent to traditional therapies or a least perform as a good addition to a patient's current treatment plans (Yates et al., 2016). Researchers have also attempted to use serious gaming concerning vaccines.

Although an effective and proven method of preventing infectious diseases, vaccination has faced hesitancy by the public because of a retracted paper linking autism and the measles, mumps, and rubella vaccine (Rao and Andrade, 2011). Since the release of that paper in 1998, researchers and public agencies have attempted to improve public opinions towards vaccines. Over two decades later, doubt of vaccines' efficacy and utility still exist. It is here where researchers are hoping serious gaming can be helpful to vaccines. It is thought that by implementing vaccines into serious games, the games can act as an educational tool for public health (Ohannessian et al., 2016). Tiltfactor laboratories took a slightly different approach to educate the public on vaccines through their serious game-POX: Save the People (Flanagan et al., 2011). The game explores anti-vaccination moments' consequences and educates the player on herd immunity and the need to vaccinate. Some researchers believe that serious gaming can be more than just a tool to improve public opinion but as a vaccine itself. Dennis D. Embry's work on making the Good Behavioral Game a universal behavioral vaccine is one example (Embry, 2002). In addition to serious games' potential as disease prevention tools and therapeutics, games have also found utility throughout the DDP.

Games have found utility throughout the DDP. For example, Foldit, an online puzzle game about protein folding, has led to several scientific breakthroughs by harassing community science in an online free access game. In 2010, Foldit provided insights that solved the crystal structure of M-PMV retroviral protease, an enzyme involved in

reproducing HIV in just three weeks (Khatib et al., 2010). In 2011, Foldit players developed an energy optimization algorithm for protein folding that had significant similarities to the unpublished algorithm scientists were developing (Khatib et al., 2011). These algorithms showed considerable improvement compared to the benchmark algorithm Classic Relax used within the Rosetta structure prediction and design program. The scientist developed algorithm -Fast Relax- went on to be implemented into all Rosetta de-novo and homology modeling methods. In addition to these discoveries, Foldit monomer design puzzles have also led researchers to develop a potential new approach for designing proteins (Foldit Staff, 2020). In light of the COVID-19 pandemic, researchers are also attempting to use Foldit to discover a protein to bind to the interleukin receptor to treat the cytokine storm found in advanced COVID-19 patients.

In the next section examples of serious gaming in other industries is provided.

4.3 Serious Gaming in the Other Industries

The world of technology, including technology transfer and cybersecurity, has also gained insights from gaming (Henry et al., 2017; Kumar and Bhuyan, 2019). RAND Corporations' serious game 360 was initially created to address the Defense Advanced Research Projects Agency (DARPA) challenges with technology transfer. 360's capabilities and success allowed for its use in other endeavors, such as successfully being applied to develop a cybersecurity framework for the Hewlett Foundation (Henry et al., 2017). The objective-driven game brings together stakeholders, subject-matter experts, and hands-on operators to reveal solutions to target problems. Between 30-60, players are split into groups to solve smaller elements of the larger target problem. Pinning players against a scenario, the game is intended to provide necessary insights for decision-makers when

other analytical tools cannot be leveraged (Henry et al., 2017). Politics and policy have also been simulated in serious games, although typically for educational rather than problem-solving purposes.

The political game Peacemaker by Impact Games educates players on conflict resolution by challenging its players to bring peace between Israeli and Palestinian conflict (Impact Game Staff, 2020). This is done by casting players as either the Israeli Prime Minister or the Palestinian President. Once cast a role, players are presented real news footage and images for events occurring in the Middle East that the player must make decisions on. A Force More Powerful, documentary turned serious game is another example of political education through gaming (Staff, 2006). The game released in 2006 was co-produced by The International Center on Nonviolent Conflict (ICNC), and York Zimmerman Inc set out to teach players nonviolent strategies to overcome real-world adversaries (e.g., corrupt rulers). Although no longer supported the game's sequel, People Power: The Game of Civil Resistance has a similar goal and is still actively supported (MAROVIC et al., 2015). Another noteworthy serious game is IBM's IBM City One, a city-building simulation designed to help IBM clients understand the potential of innovative and sustainable solutions in areas of energy, water, retail, and banking (Grant, 2010). The game released in 2010 provides a venue for policymakers and regulators to explore solutions that can be implemented into their daily work by placing players in charge of realistic city development decisions. Players start with one of the four industries and eventually move into all four while considering the city's revenue, profit, citizen satisfaction, and environmental betterment. As the player progresses, a series of crisis scenarios are presented that force the player to balance economic, ecological, and

sociological concerns. In making their decisions, players can then explore the consequences of innovative and sustainable solutions through the game that would otherwise be too difficult and costly to explore.

4.4 Conclusion

Serious gaming has begun to take a foothold in pharmaceutical problem-solving. Companies such as Akili's Interactive are seeing success in the form of positive clinical trial results and FDA approval for digital therapeutics. Academic researchers have begun exploring novel uses for serious gaming in the way of protein design and more with promising results. Additionally, game repurposing- repurposing a game originally intended for entertainment into a serious game-has been explored in games such as Minecraft and America's Army also with promising results. Other possible games with repurposing potential are games such as BigPharma by Twice Circled and Klabater, which immerse players into a realistic and decision-making pharmaceutical environment and can be easily modified. Regardless of the method used rather through novel development or game repurposing, serious gaming applications can only expand as the gaming industry grows, and U.S. universities begin opening serious and esport gaming departments. This chapter has shown the utility of serious gaming as a tool for problem-solving while empathizing its applications in the pharmaceutical industry. A review of serious gaming as a digital treatment has been provided along with serious gaming applications in other sectors.

CHAPTER 5. MONETARY INCENTIVES FOR PRODUCING COUNTERFEIT, ADULTERATED, AND MISBRANDED MEDICINE: CASE STUDIES AND EXAMPLES

5.1 Introduction

In 1996, Ritonavir was approved to market as a protease inhibitor ("Ritonavir, Abbott protease inhibitor, approved.," 1996). By 1998 Abbott Laboratories was facing a potential financial crisis as a less soluble polymorph (Form II) of Ritonavir was discovered (Bauer et al., 2001). Forming during the manufacturing process of Ritonavir, Form II resulted in a temporary cease of Ritonavir sales. In addition to the loss in sales and ticking clock on patent life protection, Abbott Laboratories also faced additional development costs (Aldridge, 2007; Bauer et al., 2001). Abbott Laboratories scientists ultimately found methods to avoid the polymorph formation, and Ritonavir returned to market. Nevertheless, Abbott faced a significant financial burden due to this unexpected event.

Ritonavir's unforeseen polymorphic change is an example of the complexities and risk involved in pharmaceutical development. Since then, analytical techniques such as Raman spectrometry, solid-state nuclear magnetic resonance, and x-ray diffraction are used to spot polymorphs existence before a drug is approved (Bauer et al., 2001). Further computational modeling for predicting polymorph existence is seeing success (Piaggi and Parrinello, 2018). However, these techniques can only be helpful if the company (humans) involved are honest. Such seems to be the case with Abbott Laboratories' handling of Ritonavir. Unfortunately, companies (humans) are not always honest in burdensome scenarios. As Abbott Laboratories learned, being honest is potentially expensive in both time and money. Often incentivizing humans to decide a dishonest, unethical, and possibly fraudulent path.

When companies face difficult events, the humans leading those companies must decide to act ethically or unethically. When a dishonest path is chosen, fraud is often the result. Fraud can be described as an intentionally deceitful action intended to provide dishonest gain (Chen and James, 2021). Criminology tells us that in order to effectively detect fraud, pursuers must know why it's committed (Kassem and Higson, 2012). Famous criminologist, Donald R. Cressey's Fraud Triangle Theory shines light on this topic. Theorizing that for fraud to occur, three elements must be present-incentive, opportunity and rationalization (Cressey, 1973). Examining the pharmaceutical industry through the fraud triangle, we see the ideal environment for fraud emerge.

Incentive: The pharmaceutical industry's 2006 global sales raked in approximately $634 billion. A value almost doubled from 2001 global sales of $387 billion (OECD, 2008). In 2010, counterfeits (defined below) were worth an estimated $75 billion. Moreover, the profit margins for counterfeits are reported higher than illicit drug trafficking (Chambliss et al., 2012). For example, counterfeit sildenafil (Viagra) is estimated to be nearly ten times more profitable than street heroin (Everts, 2010), and nearly 2000 times more profitable than selling cocaine (Bingham, 2009). Providing plenty of monetary incentives for criminals. Indeed, actual criminals bypassing regulation and supply expenses, may gain 3000% in increased profit margins than those who don't (Blackstone et al., 2014).

Opportunity: The globalization of the pharmaceutical industry has added complexity to the pharmaceutical development process and supply-chain (Luis Valverde, 2016). Further, the nature of the products is complex. Often requiring specialized equipment

to detect contaminates (Campbell and Lodder, 2021c). Collectively the complexity from the products and supply-chain make detecting counterfeit, adulterated, and misbranded medicine difficult. Hence, providing a low-risk, high-opportunity environment for fraud.

Rationalization: Pharmaceuticals are sensitive in nature, which means life or death for many patients. This sensitivity may provide bad actors with the feeling they are doing good by providing vital products. Even if a few corners are cut, the important thing is the customer gets their drugs, right? Further, a unique relationship with regulators exists. Possibly allowing bad actors to rationalize avoiding penalties for their actions. For example, imagine a company producing an angiotensin II receptor blocker such as Valsartan is cited for policy incompliance. Regulators are then trapped in a regulator's dilemma. Shut the facility down until the violation is corrected. Therefore, risking a drug shortage in which thousands of patients could suffer (Jackevicius et al., 2020). Or allow the facility to continue producing the product with an agreement that the facility will fix the problem moving forward. With the latter option the most typical choice, the regulators are left having to rely on good faith alone. Allowing room for bad actors to easily rationalize penalty avoidance even if detection were to occur. Of course, this example is simplified. Indeed, regulator's dilemmas can be highly complex (Schilsky, 2018). Yet, the point remains. Pharmaceutical suppliers have a unique advantage over regulators. Hence, the sensitive nature of pharmaceuticals provides an environment for fraudsters to rationalize their bad actions.

Satisfying each element of the fraud triangle the pharmaceutical industry provides an ideal environment for fraud to manifest. Pharmaceutical fraud is overarching and often refers to several unethical or dishonest acts. Indeed, it is not easy to define and has yet to find a universal definition. Health drug frauds, which are drug products that claim to treat disease or improve health with unproven effectiveness (FDA, 2016b). And current good manufacturing practice (cGMP) incompliance in which pharmaceutical manufacturers knowingly (or unknowingly-this aspect being somewhat irrelevant as it is their legal responsibility to know) distribute low-quality products or fail to take the actions required to ensure quality (Rovira and Espín, 2009) are only two examples of what may be termed pharmaceutical fraud. To further complicate the ambiguous terminology, pharmaceutical counterfeiting, a common pharmaceutical crime, has found several definitions. For example, the world health organization (WHO) defined counterfeit medication as "one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and, counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging." (WHO, 1999). While the FDA has simply referred to counterfeit drugs as "fake medicine" that may be harmful to one's health (FDA, 2011a). Further, WHO's attempts to update their definition have provided more confusion. Leading authors to often revert to the 1999 definition (Acri, 2018; Deisingh, 2005). Keen readers may have already noticed the overlaps in the WHO's 1999 definition of pharmaceutical counterfeits and the FDA's 2016 definition of health drug frauds. Nevertheless, for the purposes of this chapter, pharmaceutical fraud will be loosely defined as any intentionally deceitful action intended

to provide dishonest gain through or related to pharmaceuticals and will be used to describe the actions which result in CAMMs. And unfortunately, CAMMs are a growing problem.

Pharmaceutical fraud is a growing issue. Indeed, WHO estimates that nearly 10% of the global pharmaceutical trade is counterfeit (Williams and McKnight, 2014). Further, counterfeits are no longer just an issue in developing regions of the world but a global concern (Wertheimer et al., 2003). In 2012, it was estimated that approximately 1% of drugs in the US were counterfeit, with an expected increase to occur annually (Chambliss et al., 2012). Though 1% seems negligible, Chambliss points out that if a pharmacy distributes 200 prescriptions a day. Two may be counterfeit (Chambliss et al., 2012). Recently, Valisure located in Connecticut reported that nearly 10% of the drugs tested have been counterfeit, adulterated, or misbranded (Valisure, 2021a). Meaning out of 200 prescriptions 20 may be substandard. In other regions of the world, counterfeit drugs can make up to nearly 50% of the region's supply (Wertheimer et al., 2003; Williams and McKnight, 2014). In 2011, 64% of anti-malaria drugs in Nigeria were counterfeit (Blackstone et al., 2014). A quality assessment study of 7 cardiovascular drugs in 10 sub-Saharan countries found that of 1530 drugs tested, 249 were of poor quality. With amlodipine having the highest prevalence with, 87 of 305 samples deemed substandard. The study concluded that nearly 1 in 6 samples were counterfeit (Antignac et al., 2017). Truly pharmaceutical frauds are not a victimless crime. Indeed, reputable companies, partners, and patients are victimized.

CAMMs are particularly damaging to the reputable company. Indeed, piracy and counterfeits cost US companies nearly $200 billion annually and cost 750,000 jobs (Blackstone et al., 2014). Damages such as these have motivated companies to join the

fight against counterfeits. For example, Pfizer's partnership with law enforcement has prevented approximately 226 million counterfeits from reaching markets since 2004 (Pfizer, 2020). Additionally, Medsaf, a vitamin turn medicine manufacturer, has partnered with over 500 pharmacies and 100 hospitals to provide genuine medication to regions across Nigeria (Adeshokan, 2018). Though a great start, even one CAMM can be disastrous.

Pharmaceutical frauds can have catastrophic consequences for patients. In 2008, heparin batches possessing cheap contaminates in replacement of the API reached consumers. This resulted in a national recall but came too late for an estimated 83 patients who lost their lives (Blackstone et al., 2014). Similarly, 120 hospital patients in Pakistan lost their lives to contaminated Isotab. The isotab was reportedly contaminated with anti-malarial pyrimethamine causing rapid white blood cell depletion in its victims (Arie, 2012). Reports claim that CAMM kill nearly 100,000 annually in sub-Saharan regions alone (Adeshokan, 2018). A number that continues to rise (Atabong, 2021). Globally more than 500 children have died due to cough syrup contaminated with ethylene glycol (Liang, 2006). Nearly 155,000 children die annually due to poor-quality anti-malarial drugs (Nayyar et al., 2019). While 100,000 children's deaths occur annually due to poor quality pneumonia treatments (Sample, 2019). Making matters worse pharmaceutical frauds may be harming patients in unforeseen ways. Such as its contribution to antimicrobial resistance (Nayyar et al., 2019). Clearly, pharmaceutical fraud is a critical problem resulting in illness, loss of jobs, and loss of life. A problem only exacerbated when legitimate companies are involved. This topic will be covered through several case studies. But first to gain a deeper

understanding of the problem, the next section provides several examples of pharmaceutical frauds. This is followed by the case studies section before concluding.

5.1.1 Examples

The remaining part of this section aims to briefly discuss several examples of pharmaceutical fraud. Let us begin our discussion with a fraud previously mentioned-counterfeiting.

5.1.1.1 Counterfeiting

As mentioned in the Introduction, counterfeiting has found several definitions. Making matters worse, countries ' legal definitions of what makes a drug counterfeit remain misaligned. Meaning what may be legal in one country is not necessarily legal in another. A cause for concern in a globalized supply chain. Nevertheless, for the sake of this article, we will revert to the WHO's 1999 definition. Which was prompted after 771 reports of counterfeits were reported between 1984-1999. With nearly 78% of these reports coming from developing countries (Deisingh, 2005). Since then, the number of counterfeit incidents has continued to increase in developing countries. Indeed, the WHO estimates that 1 in 10 medical products in low to middle-income countries are counterfeit (WHO, 2019). With the internet playing a key role in the scale-up of counterfeits through means of falsified pharmacies and delivery drug deals (O'Hagan and Garlington, 2018). Counterfeit drugs are a critical issue in more developed countries as well.

In 2016, 1,579 North Americans experienced seizures related to taking counterfeit medicine (Acri, 2018). Further, North America is facing an alarming increase of illegally trafficked Fentanyl-laced counterfeits at the time of this writing (DEA, 2020). Fentanyl-laced drugs such as Oxycodone and Xanax add to the growing number of overdoses and

deaths related to counterfeit medicine in the illegal drug markets (Castillo, 2021; Moss, 2021; US Department of Justice, 2020). Indeed, counterfeit drugs can be dangerous. Further counterfeits can also be damaging to the drug supply itself.

Beyond breeding an environment of mistrust. Reputations of respectable manufacturers are on the line, as well as brand integrity. Indeed, victims of counterfeit drugs have filed lawsuits against the respectable company for not safeguarding products against tampering (Deisingh, 2005). CAMM's sourced by reputable manufacturer make solving the problem even more difficult. For example, researchers at the University of Kentucky (UK) found that 2 of the 3 companies supplying Acetazolamide to the UK hospital were contaminated and only contained 80-87% of the labeled API amount (Chapin and Willett, 2021). Though the root cause of this issue is still unknown, it may be speculated that the drug product originally contained the labeled amount and degraded over time. If this is the case, a cGMP incompliance may be to blame as these batches of Acetazolamide should have never reached the pharmacy. This leads to the next example-cGMP incompliance.

5.1.1.2 cGMP incompliance

cGMP is a set of practices designed to ensure quality in pharmaceutical manufacturing (Campbell and Lodder, 2021c). GxP extends these practices to x=distribution, clinical, laboratory, and other settings. cGMP and related GxP practices are among the most violated pharmaceutical guidelines (Rovira and Espín, 2009). Though most violations are likely accidental and typically corrected before much harm is done. Not all violations fall under the accidental category. PharmaTech LLC for example, went through numerous inspections and warnings yet still failed to correct cGMP violations (FDA, 2012; Huntington et al., 2016). PharmaTech's inaction allowed for *Burkholderia cepacia (BC)*- an opportunistic pathogen with the capacity to cause serve respiratory

illness- growth in the facility's water system (Tavares et al., 2020). The same water system was used to formulate the companies over-the-counter (OTC) Dicto Liquid stool softener (Lalama et al., 2016). After infecting several the FDA called for a national recall (Kerr, 2017). Though the damage was done, and PharmaTech would face a lawsuit for the death of a 10-month-old infant. A case that PharmaTech settled in 2020 (Fischer, 2020).

5.1.1.3 Delaying Generics

Innovator drug companies facing patent expiration may delay generic market entry by suing the generic producers. By calming allegations that the generic company has infringed on the innovator's patents; innovators can delay market entry by 30 or more months (Rovira and Espín, 2009). Indeed, the most common delay of generic entry is patent ligation (Dave et al., 2020). Allowing the innovator to have additional exclusivity on the market that more than compensates for the legal cost of the trials (Feldman, 2017; Rovira and Espín, 2009). Although this tactic is not necessarily fraud per say it is gaming the Hatch Waxman Act (Feldman, 2017) and is estimated to be costing Medicard millions (Dave et al., 2020). Additional methods for delaying generics include refusal of product samples which are needed to prove bioequivalence (Feldman, 2017).

5.1.1.4 Price Hikes

Between 2009 to 2016, Mylan raised EpiPen prices by more than 400% (Carrier and Minniti, 2017). Resulting in the epinephrine delivering device costing over $600. When the medicine itself only cost pennies per dose (Carrier and Minniti, 2017; Glabau, 2017). Further, Mylan misclassified EpiPen as a generic instead of a branded drug. Resulting in Mylan paying lower rebates to the government (SEC, 2019). In essence, withholding millions of rightly owed funds from Medicaid. Mylan settled the violation against the False Claims Act by agreeing to pay $465 million (US Department of Justice, 2017). Further,

Mylan refused to work with government investigators throughout the investigation process. Specifically failing to disclose or accrue for losses relating to the investigation (SEC, 2019). This time Mylan agreed to pay $30 million to settle the disclosure and accounting failures (SEC, 2019). Mylan's EpiPen prices are not necessary fraud, but they are arguably unethical as they limit access to lifesaving medicine. Other examples of price hiking are Daraprim's 5000 percent increase by then Turing Pharmaceuticals (Luthra, 2018) and Novartis' one-time injection for spinal muscular atrophy that costs $2.1 million, Zolgensma (Lupkin, 2019a). Even insulin has been targeted with manufacturers facing recent lawsuits over alleged price fixing (Anderson, 2020; Sagonowsky, 2019).

5.2 Method

The potential for monetary gain through unethical or fraudulent acts is examined in four case studies. These studies focus on legitimate companies that opted a dishonest path. The studies include - purchasing and distributing from unlicensed sellers, unlawful promotion of Paxil, Wellbutrin, and Avandia, and concealing knowledge of cancerous risk data. Financial and economic information is gathered through mining the US Department of Labor Statistics, govinfo, US Securities and Exchange Commission, and US Department of Justice databases.

5.3 Results

CAMM are a serious threat to the PSC as they are difficult to detect and can by life threatening. CAMMs become an even larger threat when they are sourced through reputable companies. To shine light on this topic and provide an understanding of the problem and its respective monetary motivates this section examines the economics and potential monetary gain surrounding four cases of pharmaceutical fraud. Examined cases included-purchasing and distributing from unlicensed sellers, unlawful promotion of Paxil,

Wellbutrin, and Avandia, and concealing knowledge of cancerous risk data. For each case, an economic screenshot is provided which summarizes potential pressures, motivates, and goings-on during the time of the event. Further, sub-titles are hyperlinked to the case's corresponding mini game such that the reader may gain an understanding of gaming models' ability to capture a range of scenarios.

5.3.1 *Purchasing and Distributing from Unlicensed Sellers*

A unique scheme was developed by Cumberland Distribution, Inc., ("Cumberland"), a wholesale prescription drug distributor licensed in Tennessee (TN). The company knowingly bought prescription drugs from unlicensed "street sellers" (Middle District of Tennessee, 2013). Purchasing took place in New York and Miami through a network of individuals with legitimate prescriptions. Drugs entangled in this scheme include immunodeficiency virus/acquired immunodeficiency syndrome, antipsychotics, antidepressants, blood pressure, and diabetes treatments (Middle District of Tennessee, 2013; Roth, 2021a). Once purchased the drugs were then shipped to Cumberland's warehouse located in Nashville, TN. Here the drugs underwent cleaning, organizing, and repacking before being sold and distributed to independent pharmacies. Those involved attempted to evade authorities by setting up private emails, purchasing burner phones, and renting another warehouse (Boling, 2018a). Red flags surrounding the Cumberland case included a number of reports claiming drug bottles contained the wrong medicine, incorrect labeling, and foreign objects. Several reports also claimed at least one bottle contained tic-tacs instead of medicine (Boling, 2018b).

The Cumberland's economic screenshot surrounding this case is:

- The crimes occurred between December 2006 to August 2009 (Middle District of Tennessee, 2013) in Nashville, TN; Miami, Florida; and New York, New York. During this time, the US was facing an economic recession in which over 8 million jobs were lost (Barello, 2014). This may have given individuals an incentive to sell their drugs cheaply for extra cash. Worth noting some studies suggest American's pharmaceutical sales went up nearly 12% during the recession (Buysse, 2010).
- Unemployment rates peaked at around 10% during this time (Cunningham, 2018).
- Pharmaceutical companies conducted large-scale layoffs. For example, Pfizer laid off over 1,000 employees in 2009 (Buxton, 2019).
- During this time, raw material imports costs increased (Buysse, 2010).

The scheme resulted in the company grossing over $50 million in proceeds. Resulting in over $14 million in profit. Criminal charges were brought against the company's President and two co-workers. Cumberland's President was found guilty of Mail Fraud. The President was made to forfeit $1.4 million and was sentenced to six years in prison. Further, the court ordered restitution payments totaling $3,386.08 to two pharmaceutical companies (Middle District of Tennessee, 2013).

5.3.2 *Unlawful Promotion of Paxil, and Wellbutrin, and Avandia*

In 2012, GlaxoSmithKline (GSK) pleaded guilty and agreed to the largest pharmaceutical fraud settlement in US history at the time (Office of Public Affairs, 2012). The settlement was a result of GSK's unlawful promotion of Paxil, and Wellbutrin. Along with the failure to disclose clinical safety data of the diabetes drug Avandia (District of Massachusetts, 2012). Court documents reveal claims that between January 1, 1998, to

December 31, 2003, GSK promoted off-label uses of Paxil. Between January 1, 1999, to December 31, 2003, GSK knowingly promoted Wellbutrin for off- label uses (e.g., weight loss and sexual dysfunction) and at dosages other than those for which its use was approved as safe and effective by the FDA (Ortiz, 2012). Further claims made in the settlement involved the asthma medication Advair being unlawfully promoted between January 1, 2001, to June 30, 2010, concerning dose. Lamictal between January 1, 1999, to December 31, 2003, being promoted off-label. Zofran between January 1, 2002, to December 31, 2004, being promoted off-label. And a kickback scheme involving Praxil, Wellbutrin, Advair, Imitrex, Lotronex, Flovent and Valtrex (Ortiz, 2012).

Focusing solely on Paxil, Wellbutrin, and Avandia, the economic gain of GSK's actions was enormous. Though difficult to separate the "honest" profit from dishonest profit, one can gain an idea from looking at the sales during the years covered by the settlement and the fine given. Here is a screenshot of GSK sales during the settlement period.

- Paxil brought in $11.6 billion in sales.
- Wellbutrin brought in $5.9 billion in sales.
- Avandia brought in $10.4 billion in sales (Sifferlin, 2012).

GSK agreed payout is as follows.

- GSK agreed to pay $1 billion in criminal penalties. The $1 billion criminal fine was broken down as follows.
    - $159,768,000 for the unlawful promotion of Paxil.
    - $554,433,600 for the unlawful promotion of Wellbutrin.
    - $43,185,600 criminal forfeiture for Paxil and Wellbutrin.
    - $242,612,800 criminal fine for Avandia.

- GSK agreed to pay $2 billion in civil damages to federal and state healthcare programs. The $2 billion dollar fine for civil damages was broken down as follows.
    - Federal Recovery: $1,501,618,568.
    - State and Public Health Service (PHS) recovery: $498,381,432 (Ortiz, 2012; US Department of Justice, 2012).

The GSK'S economic screenshot between 1997 to 2010 is:

- Zantac's market exclusivity was terminated in July 1997 (Bendt et al., 2002). Until this date Zantac was bringing in the Glaxo Wellcome company nearly $1.6 billion in U.S revenue annually (Moore, 1997).
- Asian financial crisis began in 1997.
- The early 2000s recession covered approximately 1 year of the settlement range. Further, this recession was noted for its general decline in exports. Along with a decline in businesses investing in structures and inventories (Kliesen, 2003).
- The US was facing the great recession in approximately 2 (2007-2009) of the ~10-12 years (1998-2010) covered (Barello, 2014). This event may have contributed to the ~£1 billion drop in pharmaceutical US sales and subsequent drop in profit in 2007 (See Figure 5.1 and 5.2).
- Augmentin lost patent protection early in 2002 with the patent meant to last until 2018. Augmentin was GSK's second largest drug in the year prior (Tesler, 2004).
- Avandia lost market exclusivity in 2008.
- Avandia experienced regulatory whiplash. In 2008, the FDA mandated the medicine come with black box label concerning increased ischemic cardiovascular

risk. This was later retracted in 2010. There is some evidence that this may have influenced patients taking it and hence sales (Hickson et al., 2019).

- Advair lost market exclusivity in 2010. However, the FDA did not approve the first generic of Advair until 2019 (Meyer, 2019).

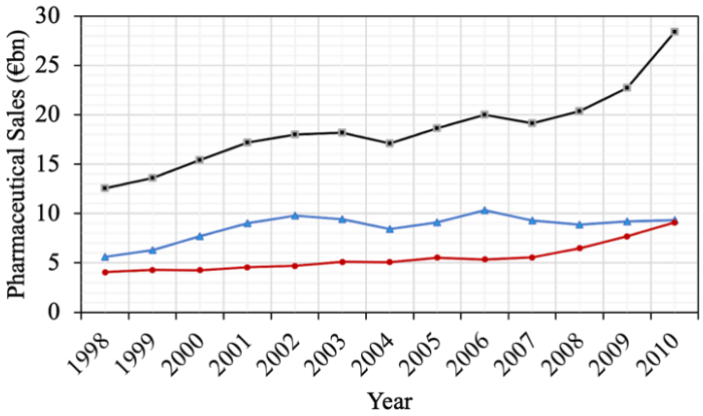

Figure 5.1 Summarizes GSK's total pharmaceutical sales (black line), US pharmaceutical sales (blue line), and European pharmaceutical sales (red line) between 1998-2010. Data gathered from GSK's annual investor reports (GSK, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2000).

GSK faced numerous patent expiration and multiple economic recessions during the time covered in the $3 billion settlement. GSK also suffered multiple negative results in clinical trials with drugs such as Praxil, lack of efficacy for depression in patients under the age of 18 (Office of Public Affairs, 2012). Further, generic introduction can cut nearly 90% of a company's sales (DeRuiter, 2012). The numerous losses of high-profit drugs during a short time with multiple recessions and negative clinical results may have incentivized the company's dishonest actions. Nevertheless, the scheme was brought to light by whistleblowers. Notably Thomas Gerahty, a former senior marketing development

manager for GSK, and Matthew Burke, a former regional vice president for GSK (Kelton and Brown, 2011; Phillips & Cohen, 2012).

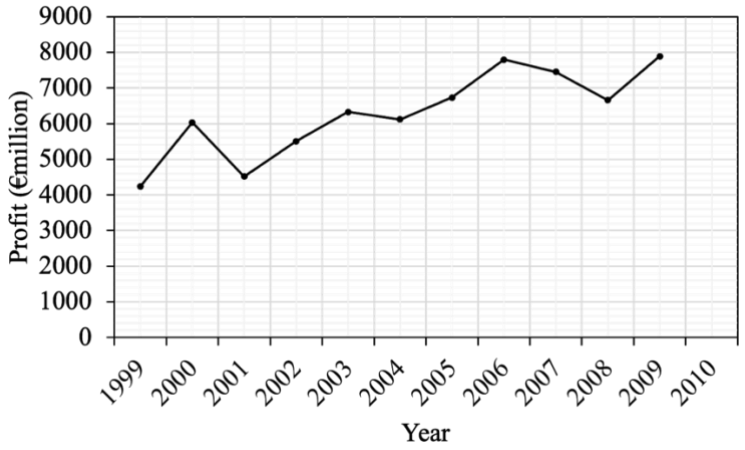

Figure 5.2 Summarizes GSK's profit before taxation by year. Data gathered from GSK's annual investor reports (GSK, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2000).

5.3.3 *Concealing cancerous risk of pioglitazone*

In 2015, Takeda Pharmaceutical agreed to pay a product liability settlement of $2.37 billion (Casseres et al., 2020). The settlement came approximately a year after Takeda and partner Eli Lilly were ordered to pay $9 billion (75% paid by Takeda and 25% paid by Lilly) for concealing knowledge of pioglitazone (brand name Actos) bladder cancer risks. Though the $9 billion quickly dwarfed to $36.8 million after appeals (Grisham and Harding, 2015). Both cases originate from a 2011 lawsuit against Takeda by Terrence Allen and Susan Allen. The allegations against Takeda were that Actos had caused Terrence's bladder cancer. However, Takeda argued that "bladder cancer *cannot* occur within one year of exposure to a causative agent (Doherty, 2014)." Despite this, the jury awarded $1.475 million in compensation to the Allens (Doherty and Magistrate Judge Hanna, 2014).

Although, the Allens were not the first to accuse Takeda of concealing knowledge they were the first to be successful in court (Sullivan, 2018). Following the Allen's success, numerous lawsuits against Takeda with similar allegations cropped up. Ultimately leading Takeda to its $2.37 billion settlement agreement. Despite the settlement, multiple studies have continued to conflict with the court's decision that Actos is associated with increased rates of bladder cancer (Lewis et al., 2015, 2011; Tang et al., 2018). Nevertheless, the FDA backs the position that pioglitazone does have the potential for cancerous risks (FDA, 2011b)

In addition to bladder cancer risks, Actos also carries a black-boxed warning. Stating the users of Actos are at an increased risk of congestive heart failure. The warning came alongside Avandia's black box warning in 2007 (Tanne, 2007). Unlike Avandia, Actos black-box label stuck. To gain a deeper understanding of Takeda during this time, let us look at an economic screenshot.

The economic screenshot of Takeda's early years to roughly 2011 is:

- 1985 Takeda began globalizing via a joint venture with Abbott Laboratories through TAP Pharmaceuticals.
- 1985 TAP begins marketing Lupron.
- 1989 TAP releases Lupron Depot.
- 1991 Lansoprazole proton pump inhibitor launches in Europe.
- 1995 Lansoprazole (brand name Prevacid) approved in the US.
- Between 1995-1999 Takeda launched several worldwide ventures including
    - Established Takeda UK in 1997.
    - Established Takeda Ireland in 1997.

    - Established a R&D and holdings group in America in 1997.
    - Established Takeda America in 1998.
    - Established a European R&D center in 1998 (Takeda, 2021).
- Actos gained FDA approval in 1999.
- In 2001, TAP agreed to pay $875 million for unlawful promotion of Lupron. This was one of the earlier settlements against the False Claims Act in the US (Girard, 2009).
- According to court documents Actos net sales between 1999 and 2012 were $24 billion dollars (Doherty, 2014).
- Novartis and TAP came to a licensing agreement for Prevacid in 2005 (Japsen, 2005).
- Actos was the world's top selling diabetes drug in 2007. This may have resulted from rival drug Avandia's link to heart attacks during the same time (Turner et al., 2021).
- Novartis gained Prevacid OTC approval by the FDA in 2009 (Novartis, 2010).
- Actos sales peaked at $3 billion in 2010 (Doherty, 2014).
- In 2011. Germany and France pulled Actos off the market (Turner et al., 2021).

From the economic screenshot above, it seems that Actos launched around the time Takeda was expanding. As an upcoming company attempting to globalize, it would seem natural to expect pressures for blockbuster developments such as Actos to exist within the company. Assuming Takeda was aware of the potential risks of Actos. The company may have been incentivized to conceal this knowledge due to the company undergoing a critical stage in its development.

5.4 Discussion

The three case studies above provide context of the links between monetary incentives and fraudulent acts. Such behavior has contributed to the industry's past reputation for holding stakeholder opinions over patients (Kessel, 2014). Though recently, the industry has had an improvement in reputation. The 2019 PatientView survey showed that 46% of patients surveyed viewed pharmaceutical companies as excellent or good- a 5% increase from the year before (Wyke, 2020). Even generic companies saw an increase in reputation from 34 to 35% (Wyke, 2020). But with nearly continuous unethical behavior being uncovered through the FDA and independent investigators such as Valisure and UK's Quality Study, will an improved reputation hold? It would seem difficult as fraudsters have targeted critically needed materials. Lacking quality controls with Remdesivir processing (Almeter et al., 2021), counterfeited COVID-19 vaccines (FDA, 2021), and contaminated hand sanitizer with Benzene (Henderson, 2021) are just a few examples. It would not be surprising for the entire healthcare sector to take a hit in reputation with such acts. So comes the question of how do we combat pharmaceutical fraud?

Many argue that in order to combat pharmaceutical fraud, the penalty must be placed on corporate executives, and it must be higher than the company simply writing a check. Instead, criminal charges directly against CEOs and executives resulting in prison sentences are suggested (Waters, 2012). However, in the US, it is challenging to convict company executives of pharmaceutical frauds. Even the infamous former CEO of then Turing Pharmaceuticals, Martin Shkreli (aka Pharma bro) was found guilty of security frauds not necessarily pharmaceutical frauds (Gizzi and Schmidt, 2017). Despite his alleged involvement with Daraprim's ongoing 5000% price hike (Siddons, 2021). Despite the challenges, conviction for pharmaceutical fraud is possible.

Insys Therapeutics founder John Kapoor and several executives were found guilty of illegal distribution of a controlled substance (Dyer, 2019). The case made history as the first time prosecutors had brought criminal Racketeer Influenced, and Corrupt Organizations (RICO) charges against pharmaceutical executives (Ortyl, 2019). The conviction sentenced John Kapoor to 66 months in the custody of the Bureau of Prisons, followed by three years of supervised release (Massachusetts, 2020). Executives involved faced lesser time with the minimum possible prison time given to Michael L. Babich, the former CEO of 2 months, but it could be as much as 30 months (Massachusetts, 2020). Further, the FDA took action against members involved. Permanently debarring former Insys executive Sunrise Lee from "providing services in any capacity to a person that has an approved or pending drug product application" (Roth, 2021b). Similar debarment notices were given to others convicted, including John Kapoor (Roth, 2020a, 2020b, 2021c). Indeed it seems that Kapoor's potential for future monetary incentives to commit fraud was stripped. However, it is yet to be seen if such punishments will decrease corporate pharmaceutical crimes.

5.5 Conclusion

Several common examples of pharmaceutical fraud have been presented. Including counterfeiting, cGMP incompliance, and more. In addition, case studies have been explored. Though each example and case studies vary in detail, they all stay linked through the monetary incentives for the actor. Assuming the companies involved in the case studies were not caught, they would have made off with billions of unjustly earned money. Findings suggest that monetary incentives are common among unethical fraud cases. Economic recessions, patent expirations, and company expansion are amongst the most

consistent economic factors surrounding the cases studied. Suggesting these variables may be predictors of potential drug quality issues.

It will be interesting to see how the industry's reputation holds up as more independent investigators join the FDA in the fight against pharmaceutical crimes. As more and more cases are uncovered, it seems there is a vital need for reform, whether in policy or punishment. Otherwise, we can expect more pharmaceutical fraud in our daily news headlines.

CHAPTER 6. DOES REWARDING QUALITY IMPROVE BEHAVIOR IN PHARMACEUTICAL PRODUCTION? -A SERIOUS GAMING APPROACH

6.1 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 (see Chapter 5). 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 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.

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.

6.2 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 6.1 and 6.2). Worker tasks presented themselves automatically while simultaneously pausing the BigPharma environment, at which point players could interact with the shell window (See Figure 6.1). 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.

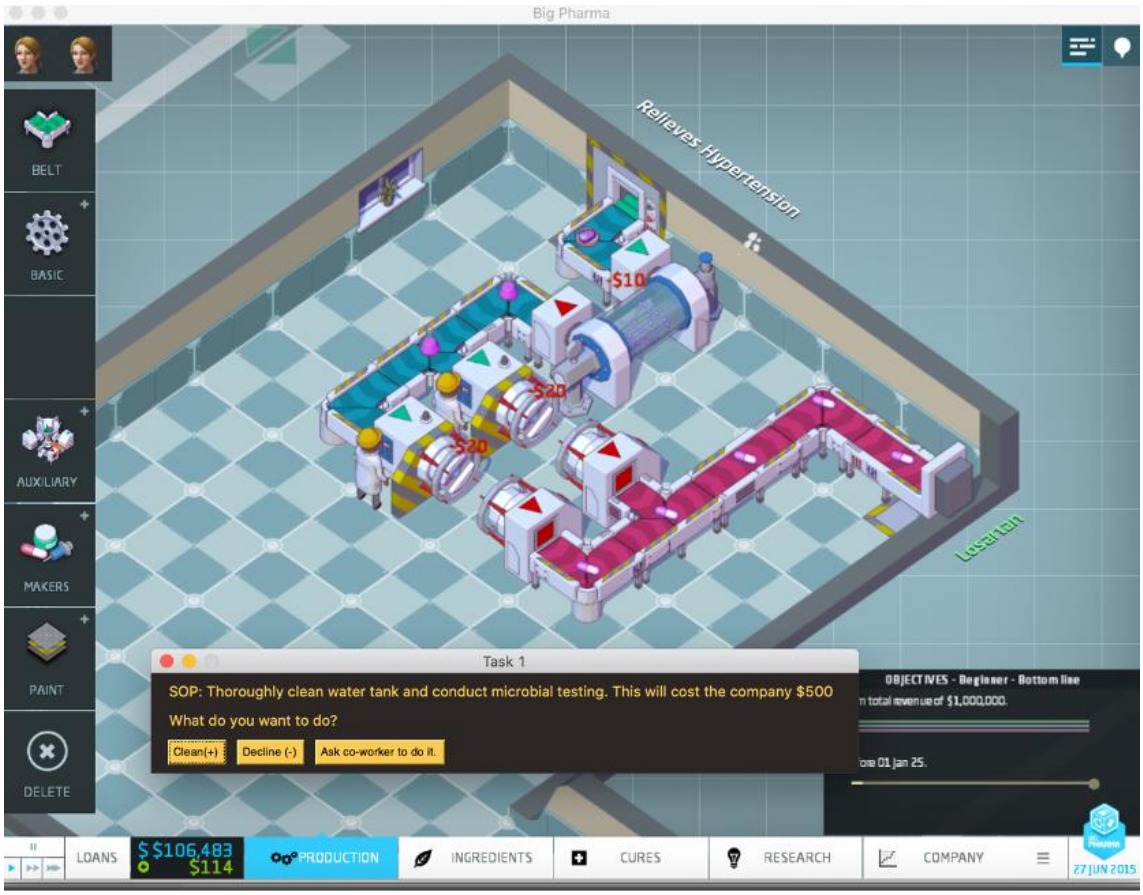

Figure 6.1 BigPharma gameplay with python shell (worker-level task) window. Shell windows were executed via Python 3-Juypter Notebooks scripts. Windows momentarily paused the game requiring input from the player before play could continue. Player's task decisions and in-game strategies were collected via program outputs and video-recordings respectively.

6.3 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.

6.4 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-Appendix 3) (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.

6.5 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 6.2 and did not vary between prompts, a fact blinded to players.

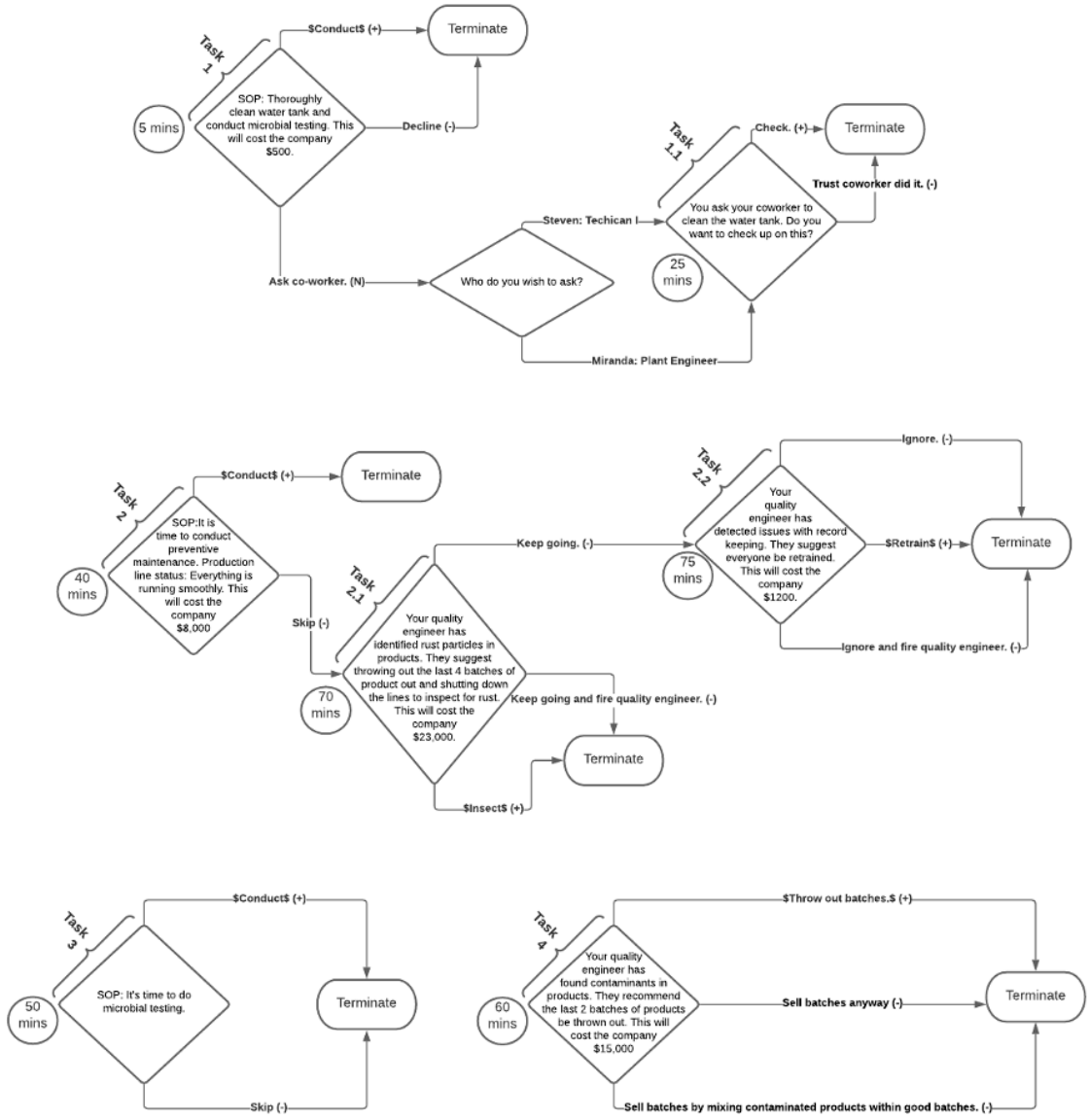

Figure 6.2 Decision trees describing the specific tasks presented to players. Where diamonds represent tasks, circles present specific time executions of respective task, and stadiums (the rectangles with rounded ends) represent the terminal points for the respective tree path. Both ethical and unethical 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 6.3) 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 6.3 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 6.4). 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 6.4.

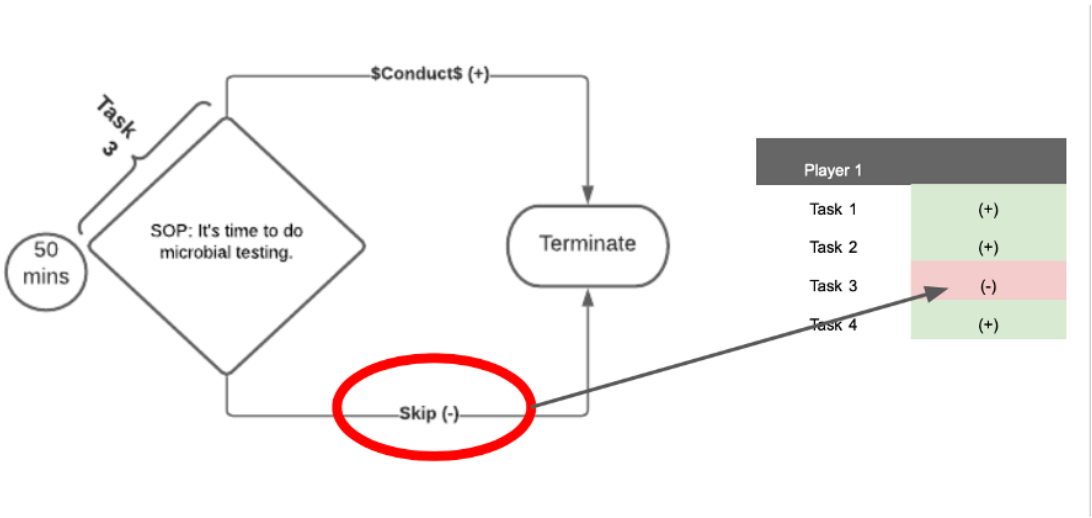

Figure 6.4 Worker Task 3 presents both an ethical and unethical approach to completion. Players' decisions are recorded through color coded tables. For this gaming session, Player 1 made ethical decisions in Tasks 1,2, and 4 represented by the green cells. For task 3 the player decided to skip the task. 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 Appendix 3-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 Appendix 3-Ethical Timetables). Using these tables players, overall strategies were described and compared against an ethical scale (See Appendix 3-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 Appendix 3-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 Appendix 3-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.

6.6 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 6.5). 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).

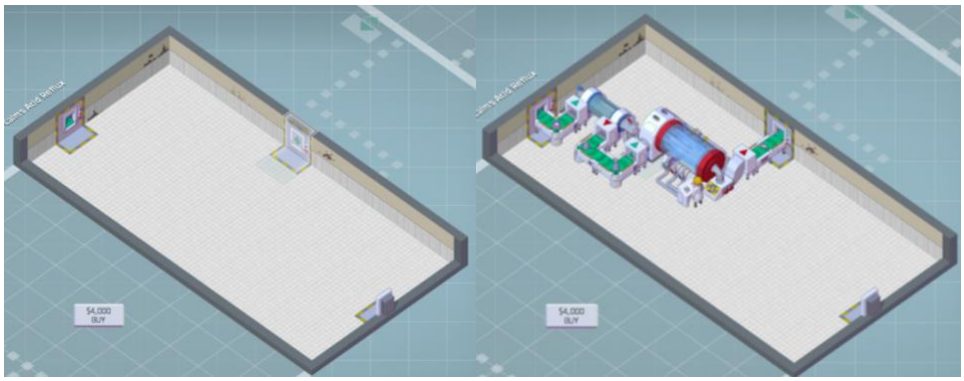

Figure 6.5 Virtual processing plant presented to players at beginning of gaming session in Prompt 1,2, and 3 (left) and control games (right).

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.

6.7 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 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.

6.7.1 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 6.6.

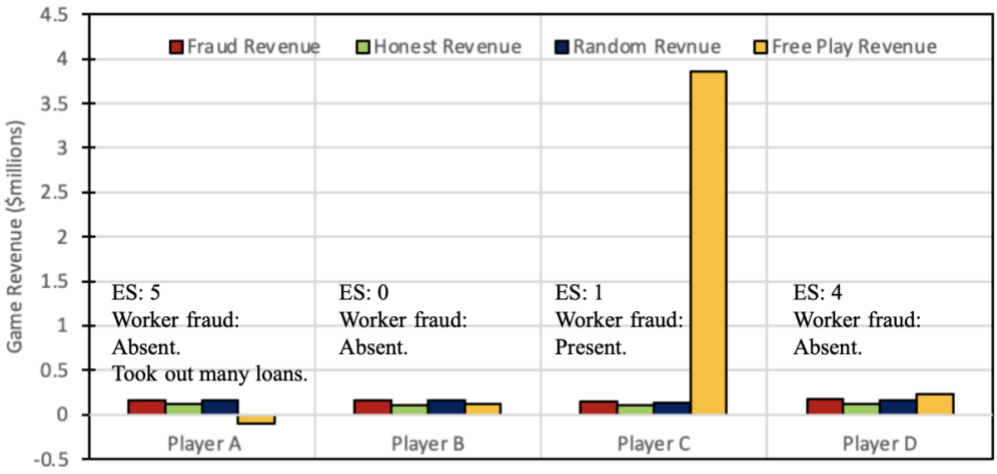

Figure 6.6 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games. Where positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), random control data are in blue (Random revenue), and players free play revenues are in yellow (Free-play revenue).

As can be inferred from Figure 6.6, 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 6.1). 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 6.1). 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 6.1 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 6.7 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 of in-game revenue, outperforming positive, negative, and random control games with an ethical management strategy.

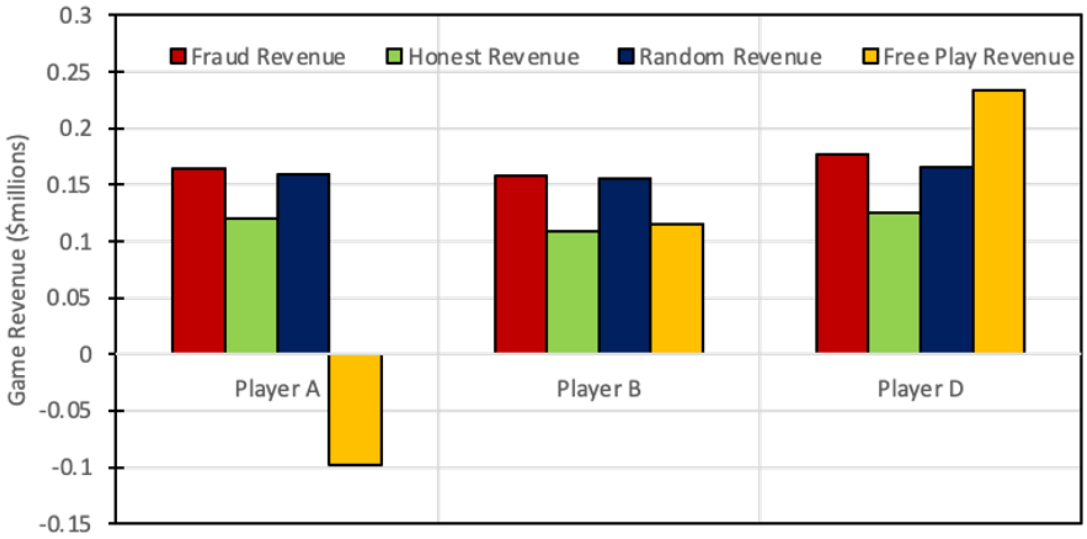

Figure 6.7 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games omitting Player C. Where positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), random control data are in blue (Random revenue), and players free play revenues are in yellow (Free-play revenue).

Further, from Figures 6.6 and 6.7, 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 6.8. 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.

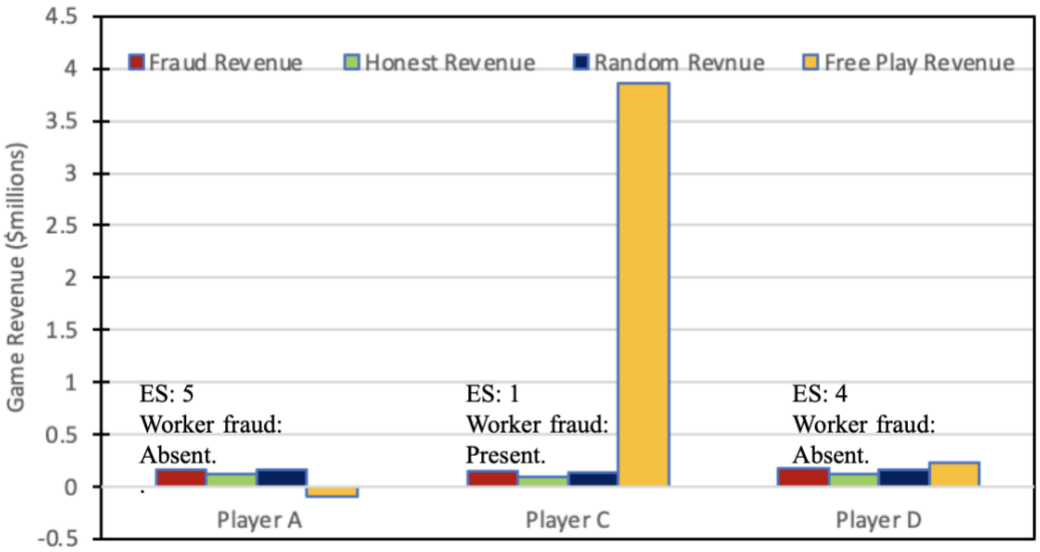

Figure 6.8 Summary of player's in-game revenue, ethical score, and shell (worker-level) decisions summary for Prompt 1 and control games omitting Player B, who effectively played a different game. Positive control data are in green (labeled honest revenue), negative control data are in red (fraud revenue), 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 6.1) was constructed comparing the players' Prompt 1 worker-level decisions to the random generator's decisions. As seen in Table 6.1, 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 Appendix 2

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.

6.7.2 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 6.9, which summarizes n=4 (one female, three male) player’s in-game revenue, ES, and worker-level decisions.

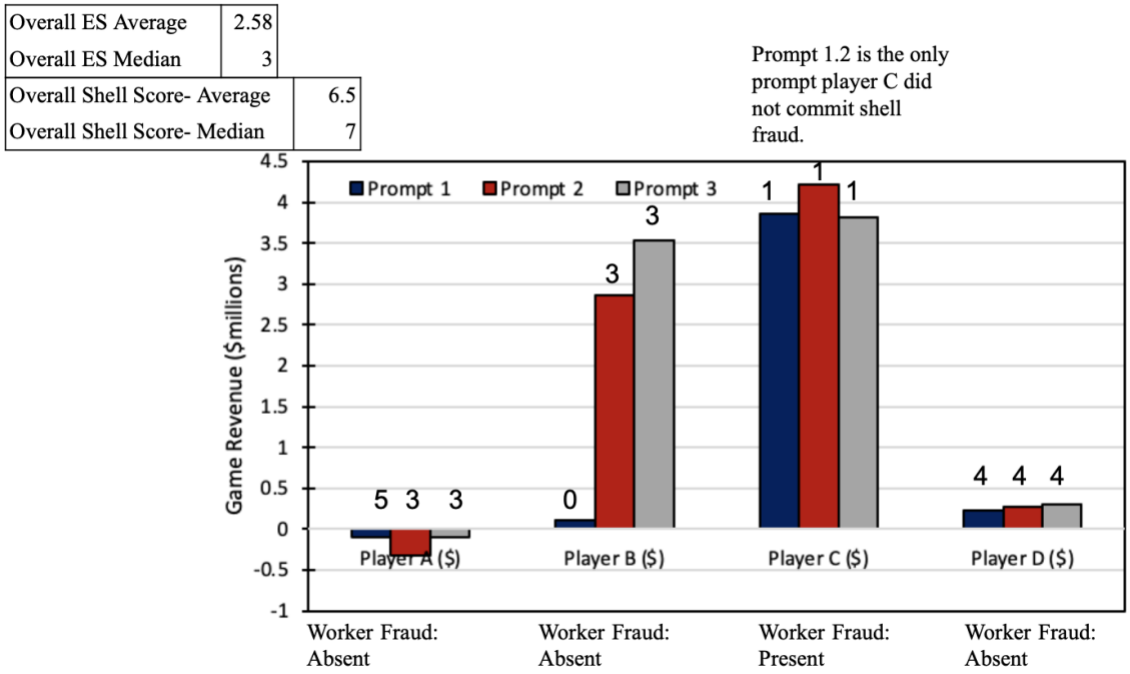

Figure 6.9 Summary of player's in-game revenue, ethical score (ES), and shell (worker-level) decision summary for Prompt 1 (blue bar), 2 (red bar), and 3 (grey bar). Ethical scores are presented over their corresponding bar. For example, Player B earned an ES of 3 in the Prompt 2 game. Further the overall 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 6.9, 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 6.9 seem likely to carry over to a real-life setting. In addition, from Figure 6.9, 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 6.8 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 6.2 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 6.3, 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 6.2 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

Table 6.3 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 6.2, 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 6.4), we see that 100% of them sold their drugs above the median (27.5%) percent markup, aka price hiking. (See Appendix 3 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).

Table 6.4 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 6.5 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 6.5).

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 6.5 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).

6.8 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.

CHAPTER 7. DOES REWARDING QUALITY IMPROVE BEHAVIOR IN A COMPETITIVE PHARMACEUTICAL PRODUCTION ENVIRONMENT? - A SERIOUS GAMING APPROACH

7.1 Introduction

Counterfeit, adulterated, and misbranded medicine (CAMM) are critical issues facing the PSC today (see Chapter 5). Indeed, current pharmacy testing flags approximately 10% of all drugs screened as counterfeit, adulterated, or misbranded (Valisure, 2021a). Further, the complex nature of pharmaceuticals makes it challenging to identify defects. Unlike fruits and other food items, there are often no rules of thumb or sensory cues to guide customers to ensure they are purchasing high-quality medicine. Instead, low-quality medicine often requires specialized equipment coupled with advanced analytical methods to be identified (Drennen and Lodder, 1990; Galante et al., 1990). It has been suggested that pharmacy-level investigators (PLIs) such as Valisure and the UK Drug Quality Study (DQS) could provide a much-needed on-the-ground (OTG) "look" or quality inspection for customers. However, PLIs OTG status typically means working with limited equipment and staffing resources. Making scanning every single drug product infeasible. Currently, a scoring system coupled with batch testing techniques helps to decide what to test now. But this does not help decide what should be tested in the future. Further, these systems can only predict what they have been trained on. Making them incapable of providing future or new ways drugs could be counterfeited, adulterated, or misbranded. Meaning PLI's and regulators alike are always one step behind.

Current scoring systems and traditional modeling can only predict based on history, where even the most sophisticated models are using data from days or weeks ago with tremendous human interference (Westman, 2020). As a result, current modeling methods

(including most AI models) often fail in the face of unexpected events such as the COVID-19 pandemic (Heaven, 2020). Indeed, COVID-19 exacerbated any pre-existing issues in the PSC and identified further vulnerabilities in drug development models, supply inventory models, and others (Adhikary et al., 2021; Buntz, 2021; Jarrells et al., 2021; Miller et al., 2021). As these models are critical to keeping the PSC running smoothly (e.g., avoiding drug shortages, ensuring high-quality medicine), it will be vital moving forward to improve on past mistakes. Though several potential solutions have been posed to solve structural vulnerabilities. Such as reshoring at least some drug production to avoid unforeseen cutoffs of vital drugs due to travel and export bans (Socal et al., 2021). There has been a notable lack in improving the behind-the-screens models, which can produce equivalent amounts of risk to the PSC as structural vulnerabilities. For example, drug shortages can come as the result of either or a mix of structural and model failures. A natural disaster at the only global supply site of a certain drug product or drug ingredient (i.e. a lack in diversity of regional production) is a structural design flaw that could result in drug shortages (Ball, 2021; Lee Ventola, 2011). But a quick shift in demand, which a supply model does not foresee, can provide just as much damage. Typically supply models provide manufacturers with a good estimate of what and how much people will be buying. Ensuring the manufacturer isn't stuck with unsold inventory. However, as Amazon and others learned in the face of COVID-19, unexpected events can alter people's purchasing quickly. Indeed, in less than five days of the COVID-19 impact Amazon's top 10 searched items all shifted in most developed countries (Westman, 2020). Most vendors on Amazon opt for Amazon to control delivery and logistics of their merchandise and typically are rewarded the top search spots. However, the sudden shift caused such heavy demands on

Amazon warehouses, that Amazon opted to alter their algorithms from vendors sourced through them gaining top result spots to vendors who took responsibility of their own deliveries appearing first among other alterations (Comrie, 2020; Westman, 2020). As Amazon is often looked at as a gold standard for logistical success, COVID-19 made clear that our current models aren't ready to face the unexpected (Bhaskar et al., 2020; Ioannidis et al., 2020).

Current models fail when unexpected events occur because they lack the human element (creativity, imagination, emotion, etc.). Gaming models bridge this gap. Indeed, games are well equipped to capture human behavior (Parsons and Wooldridge, 2002). As Naciri describes, this is because games (more specifically serious games) allow for capturing the human decisions as "they are made rather than how they should be made" (Naciri et al., 2013). That is serious gaming models allow for human decisions to be captured in order for more reliable models to be constructed. For example, Ford Motor Company has utilized a participatory virtual operations simulation to capture manager strategies around unplanned maintenance to identify ways to improve throughput (Robinson et al., 2005). Others have developed an interacting virtual emergency hospital unit to further understand Physician decision-making in the context of trauma triage (Mohan et al., 2014). In this study, Physicians interacted with the virtual emergency unit and made decisions under varying cognitive loads. It was found that physician's performance, and decision-making were consistent with their real-life actions. Further, the study found the game could manipulate cognitive load successfully and with increased cognitive loads, the players' (physicians') use of heuristics increased. A result predicted by cognitive theory (Mohan et al., 2014). In chapter 6, we saw that serious gaming have also

been introduced to provide insights into unethical behavior in the PSC that can lead to CAMMs in the drug quality game (DQG) study (see Chapter 6). In this study, Players interacted with a virtual PMB (See Figure 7.1). Representative tasks were given, and players could act in both ethical and unethical ways. Through a series of three games, players' actions were captured while being first motivated by in-game profit, second by quality, and lastly by both. The study provided evidence that incentivizing quality can promote ethical worker- and management-level decision-making. However, the study lacked human vs. human or real-life competitor effects and did not apply real-world losses to players' actions. Because of this, it is thought that players may have taken riskier actions than if these constraints were otherwise present. This chapter addresses these limitations by repeating the study in a real-life tournament format.

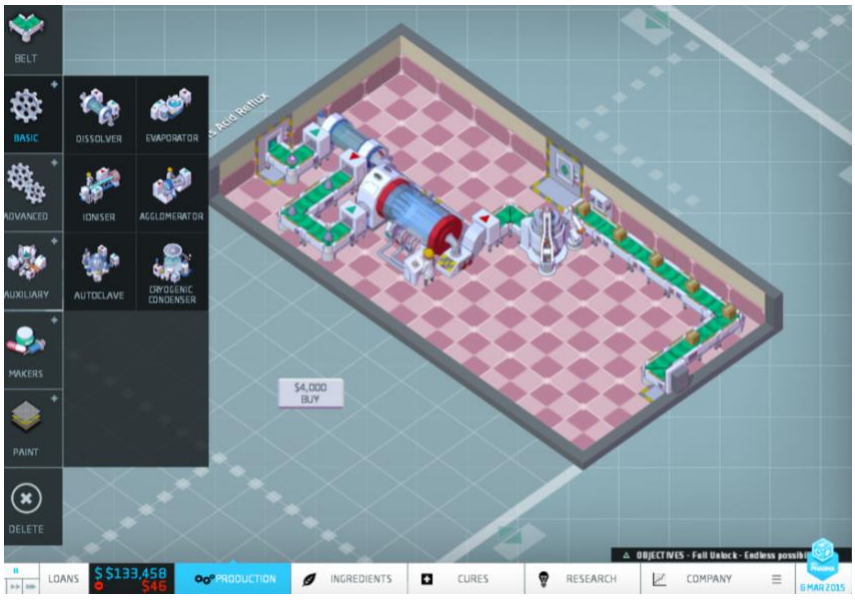

Figure 7.1 Representative BigPharma virtual pharmaceutical business. Includes marketing, processing, and research elements. Processing area shown.

The next section will illustrate the importance of competition and nothing to lose effects on behavior. A description of the tournament setup and purpose is then given (see Chapter 6). Before a brief description of the metrics used is provided. Results follow prior to addressing the study's current limitations. Future research opportunities are provided before concluding.

7.2 Competition and Nothing to Lose Behaviors

Depending on the viewpoint, competition can act as a motivator or a pressure. In specific scenarios, competition can motivate us to work harder, achieve more, and be more efficient (Bloom et al., 2013; Bracha and Fershtman, 2013). Indeed, competition has been shown to drive firms to improve relative efficiency, especially in highly competitive markets (e.g., Bertrand competition with a homogeneous product) (Hay and Liu, 1997). On the other hand, competition can act as an external pressure that fosters an environment in which humans suffer and behave unethically (Gilbert et al., 2009; Rigdon and D'Esterre, 2014). When considering what must be present for humans to partake in fraudulent behaviors, competition emerges as a potential trigger. According to criminology's Fraud Triangle Theory, three elements- pressure/incentive, rationalization, and opportunity- are required for fraud to occur (Cressey, 1973). Naturally, competition has been shown to fulfill the theories pressure element (Mackevičius and Giriūnas, 2013). An example of competition playing this role can be seen in some political elections. Indeed, the introduction of competitive candidates to political elections has been linked to electoral fraud. To the extent that the primary distribution of fraud was shown to, geographically redistributed to the central provinces, the elections took place in one Latin American study (Lehoucq, 1999). In this scenario, the incumbent has his or her political power in jeopardy while the contender has nothing to lose (i.e., everything to gain). So, it seems that in

addition to the extent of competition, the resultant human behavior may heavily rely on what there is or is not to lose. Indeed, it has been suggested that players may participate in jeopardizing behaviors in video games because there is nothing real to lose (Lodder, 2020).

Players may take part in risky behaviors in video games because there is nothing real to lose. In its simplest form, risk may be defined as the probability (of an unwanted event) multiplied by the loss (connected to the event's occurrence). Using this definition, it is easy to see why people would be willing to partake in highly jeopardizing behaviors when loss is zero (i.e., having nothing to lose). Take, for example, if you were given the opportunity to own a highly volatile stock for free. Chances are, you will be much more willing to own the stock as opposed to if you had to purchase the stock with your own funds. A similar line of thought can be used when assessing risky behaviors in video games. For example, in first-person shooters, players often run into a field or room of armed foes with bullets flying everywhere. Player's probably feel confident in doing this because they know their avatar can take a few hits (often measured by an avatar's health metric) and if they were to "die" in-game they would be regenerated (though total recklessness that results in death is often discouraged in games through forcing players to defeat foes again, repeat missions entirely, and other undesirable tasks). All in all, the player does not have all that much to lose for risky behavior. But it is probably safe to say that most of the players playing out such action would take a safer approach if the avatar were near death or could only take one bullet. Along the same line of thought, it is suspected that players of the previous DQG study may have behaved riskier than if potential loss and competition were present.

Given the above, one may infer that repeating the DQG in a tournament with a required entry fee will result in a reduction in risk-taking behavior among the players. In

the next section, a quick description of the serious gaming system, tournament setup, and games played are presented.

7.3 Tournament Setup and Purpose

How can one make video games simulate real-life better? Players can take what would be otherwise considered crazy risks within single-player video games because there is nothing real to lose and no human competition. In a tournament, players have real entry costs to lose, real cash prizes to gain, and real humans to compete against. In the previous DQG study, a non-tournament environment was utilized and suggested that players often behave more ethically when quality was rewarded. However, even with the improvement, players were observed to actively engage in what the study calls management frauds (decisions typically made at a management level). Further players were readily acting in ways that could be considered highly risky. That is, the probability of them getting caught (in real-life) would be high. The most notable action observed was players' decisions to set their prices unethically high for drugs they were selling sub-potently. Though selling sub-potent drugs may be a considered low risk, due to a low probability of detection (remembering pharmaceuticals' complex nature), price hiking drugs immediately draws attention. A lesson Martin Shkreli (aka pharma bro) found out after raising the price of Daraprim from $13.50 to more than $750 (Luthra, 2018).

In this study, a Tournament was held to determine whether the introduction of competition and real-life loss constraints changes what was observed in the absence of these real-life constraints. The games played by the players were the same as before and the RnOs were presented in the same manner through digital prompts. Prompt 1 (or game 1) was profit-focused and sought to test the hypothesis that when players are not rewarded

for quality they would act unethically. Prompt 2 shifted players' motivations to collect quality points. This prompt encouraged players to ignore money incentives and sought to test the hypothesis that when players are rewarded for quality, they would act more ethically. Lastly, Prompt 3 reintroduced the profit motive and encouraged players to maximize both quality points and in-game revenue. This prompt sought to test the hypothesis that when players are rewarded for-profit and quality, they would continue acting ethically. Furthermore, players were told that they were approved to make one and only one injectable drug as they were cast into the role of an injectable drug manufacturer in these games.

Using these games, players were recruited for an in-person tournament. Entry fees equivalent to the cost of the BigPharma game ($27.88) were required to ensure the players had "skin in the game" (i.e., incurred a monetary risk). A 1st, 2nd, and 3rd place reward were offered as $100, $50, and $30 respectively to provide a real-life reward. Where the player who earned first place had gained the most in-game revenue post the subtraction of worker task costs. Recruitment occurred for two weeks through stationery and social media (twitch) advertisements targeted towards college students. Nevertheless, recruitment was low with N=2 such that the rewards required adjustment via dropping the 3rd place position. The low turnout was thought to be a result of the Universities virtual learning status as well as the state and federal social distancing guidelines at the time of the tournament. Though the cost of entry may have provided another hurdle for some to participate.

The tournament was held for three days at the University of Kentucky's Esports Lounge located in Lexington, Kentucky. Players accessed BigPharma via PCs through

Steam, an online video gaming distribution service. The python shell, which coupled with BigPharma to provide additional human activities to the virtual environment, was integrated using Jupyter Notebooks. Players were required to play all three games (prompt 1, 2, and 3). Data was collected on these games through screen recordings and script outputs. Furthermore, players were given the opportunity to practice the first and into the second days of the event. This was to ensure all players were familiarized and comfortable interacting with the gaming environment.

7.4 Metrics

A brief description of the metrics used to describe players' behavior is given here. For more details, see Chapter 6. The players' behavior was first categorized into worker or management fraud to describe and analyze the data. Worker fraud is defined as unethical decisions made when prompted to complete tasks via the python shell and reflect decisions made by general workers. Worker fraud is quantified through a SS. Where a player's SS corresponds to the total number of worker tasks (seven) ethically completed. Hence a SS of 0 indicates a player took every shortcut possible. Where an SS of 7 indicates, all tasks were completed ethically. When calculating the SS where applicable unprompted tasks (null) are assumed to be ethically performed. Further, overall shell scores were calculated as the average or median of the players' SS across prompts. On the other hand, management fraud is described by ES and categorical descriptors. Management fraud can be thought of as decisions primarily performed by management. For example, choosing to conceal negative clinical results are typically out of the hands of workers. ES attempt to provide a description and distinction of the various players' management strategies and describe just how ethical they were or were not. To designate ES', players' specific actions were organized into timetables (See Appendix 4-Ethical Timetables) and labeled ethical or

unethical. Using these tables, players' overall management strategies were described and compared against an ethical scale (see Appendix 3-Ethical Scale) to assign the players earned ES. ES ranged from 0 to 5. Where an ES of 0 indicates the player was completely unethical (followed no RnOs). And an ES of 5 represents a completely ethical management strategy. That is, the player followed all guidelines perfectly.

7.5 Results

In the previous DQG study, the current serious gaming system was shown to be useful and capable of simulating real-life humans and their actions in a pharmaceutical manufacturing setting. Through a series of three games, the study suggested that rewarding quality could improve players' behavior in both work and management-level decision-making. Worker frauds were seen to go to zero in the presence of quality rewards, and the frequency of management frauds was seen to decrease. Despite the observed decrease in worker and management fraud, players readily partook in highly risky activities. For example, players frequently sold their drugs at unethically high prices while also selling those same drugs sub-potently. A phenomenon that interestingly reflected well with observations seen in the DQS (see Chapter 6). Nevertheless, the question has been asked - how can this serious gaming system simulate human behavior better? It has been suggested that the lack of competition and possibility of loss in the previous study may have fostered an environment of unrealistic comfort for players partaking in highly risky activities. To address these limitations, the study has been repeated in a real-life tournament that required an entry fee and provided rewards that could be won based on performance. In this way, the previous study is now constrained by competition and the probability of loss. The results of this study are presented below, beginning with Figure 7.2, which summarizes the

in-game revenue earned by players through the course of all three games (termed prompt 1, 2, and 3).

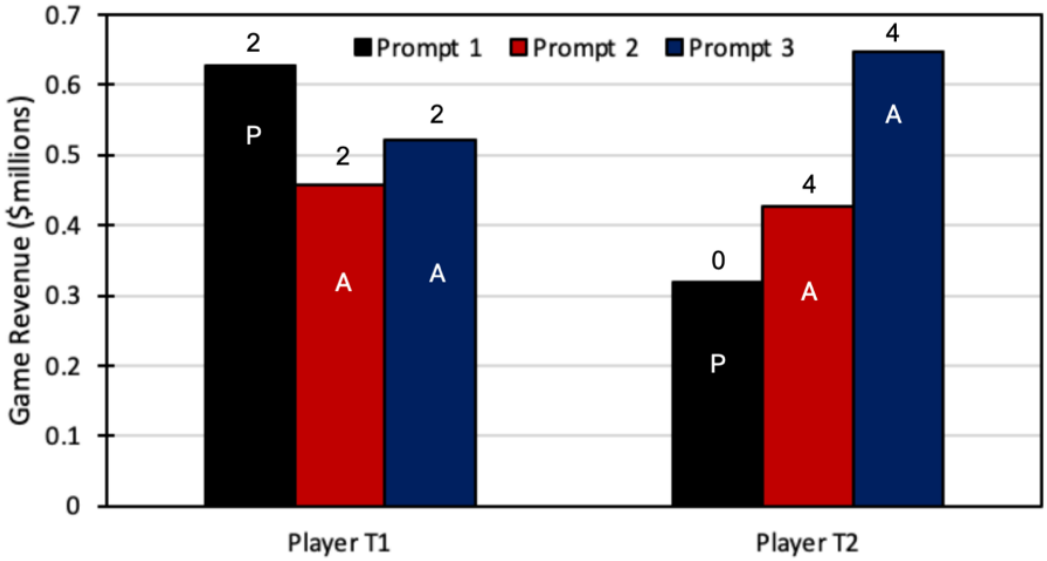

Figure 7.2 Summarizes the in-game revenue gained by players. Where numerical values above the bars are the players earned ethical score (ES). Within the bar text indicates the presence (P) or absence (A) of worker fraud.

Figure 7.2 shows that both players performed relatively well in terms of in-game revenue, with Player T1 winning first place with a total of $1,605,846, gaining $214,440 more than Player T2. Further, both players participated in worker fraud exclusively in prompt 1. This resulted in average and median overall shell score equaling 7, in Prompts 2 and 3. Agreeing well with the pre-tournament overall shell scores of 7 (average and median) in prompt 2 and a 6.75 average, 7 median in prompt 3. Therefore, suggesting that once quality rewards were introduced, players in both non-tournament and tournament settings improved worker-level decision making. Taking a closer look at Prompt 1's worker-level decision outcomes (see Table 7.1), we see that the overall average SS is 5.5.

Similar to the pre-tournament average overall shell score of 5.75. However, the pre-tournament median shell score was 7 compared to the tournament median shell score of 5.5. Suggesting that the constraints of competition and possibility of loss did not necessarily increase the frequency of worker fraud. But instead resulted in more players participating in worker fraud when motivated by profit.

Table 7.1 Summary of decision outcomes in worker-level tasks in a tournament environment. Where red indicates an unethical approach and green indicates an ethical approach to completing the task. Blue indicates the task was unprompted.

Player	Player T1	Player T2	
Prompt 1	Profit Focus		
Task 1	(+)	(+)	
Task 2	(+)	(+)	
Task 3	(+)	(+)	Shell Score Average: 5.5 Shell Score Median: 5.5
Task 4	(-)	(-)	
Task 2.1	null	(-)	
Task 2.2	null	(+)	
Prompt 1.2	Quality Focus		
Task 1	(+)	(+)	
Task 2	(+)	(+)	
Task 3	(+)	(+)	
Task 4	(+)	(+)	Shell Score Average: 7 Shell Score Median: 7
Task 2.1	null	null	
Task 2.2	null	null	
Prompt 1.3	Profit and Quality Focus		
Task 1	(+)	(+)	
Task 2	(+)	(+)	
Task 3	(+)	(+)	
Task 4	(+)	(+)	Shell Score Average: 7 Shell Score Median: 7
Task 2.1	null	null	
Task 2.2	null	null	

Additionally, from Table 7.1, we see that Player T2 earns an ES of zero for their strategy within the Prompt 1 game. Though this quickly increases to an ES of 4 in prompts 2 and 3. Interestingly this occurred in the pre-tournament results as well. Suggesting when profit motivates, some players may be more willing to prescribe their own set of rules (i.e., transform the presented game into a novel game). Indeed, the transformation of games based upon an individual's motivational profile has been previously observed. Merrick and Shafi, for example, show how classical games such as the prisoner's dilemma can be transformed into novel games by differences in individuals' motivational preferences (Merrick and Shafi, 2013).

Next, Table 7.2 presents the number of occurrences of management frauds by prompt. From Table 7.2, it is observed that the frequency of management fraud decreases in the presence of quality rewards—six occurrences in prompt 1, to 4 in both prompts 2 and 3.

Table 7.2 Occurrences of management frauds in Tournament per Prompt.

Fraud	Prompt 1	Prompt 2	Prompt 3
Sold unapproved drug	1	0	0
Sold subpotent drugs	1	2	2
Used cheap/unapproved material	2	1	1
Conceal negative clinical results	1	0	0
Price Hike by tournament median	1	1	1
	6	4	4

Further comparing the pre-tournament frequency of management frauds to the tournament in Table 7.3. It is observed that the top two most used management frauds change from price hiking and selling sub-potent drugs in the pre-tournament environment

to selling sub-potent drugs and using cheaper materials. Indeed, the frequency of selling sub-potent drugs (to be considered low risk due to the difficulty in detection) increased 25% in the tournament setting. Likewise, the use of cheaper materials (also considered a low-risk action due to the difficulties in detection) increased 25% as well. This provides evidence that under the constraints of competition and the possibility of loss players stray from riskier behavior in-game. As both selling sub-potently and using cheaper materials have a lower risk of detection compared to price hiking. Further from Table 7.3, it is observed that in a tournament, the frequency of selling entirely unapproved drugs dropped 33%. This fraud is arguably the riskiest due to the high possibility of detection and high penalties associated with the deed. Indeed, at the time of this writing, two executives of a generic drug company face indictment arising from the distribution of 383,000 bottles of unapproved hydroxyzine between 2011 and 2013 (Crandall, 2021).

Table 7.3 Frequencies management frauds took place in pre-tournament and tournament environments.

Fraud	Pre-tournament	Tournament
Sold unapproved drug	50%	17%
Sold subpotent drugs	58%	83%
Used cheap/unapproved material	42%	67%
Conceal negative clinical results	0%	17%
Price Hike	83%	50%

Lastly, a comparison of players ES' is provided in Table 7.4. Given ES are a reflection of the players' management strategies. In both pre-tournament and tournament settings, we see the emergence of consistent player scores, suggesting players form a strategy within the game and stick to that strategy moving forward (forming a habit). The

habit phenomenon in games have caught the attention of researchers; however, there is still a lack of literature concerning this topic (Schaekermann, 2016). Nevertheless, this may suggest that training people correctly and ethically early in their work-life is important. It seems that it may be worth wild for future research.

Table 7.4 Summarizes the ethical scores earned in Prompt 1, 2, and 3. Players A, B, C, and D results are from the pre-tournament sessions. While Player T1 and T2 results are from the tournament sessions.

	ES-Prompt 1	ES-Prompt 2	ES-Prompt 3
Player A	5	3	3
Player B	0	3	3
Player C	1	1	1
Player D	4	4	4
Player T1	2	2	2
Player T2	0	4	4

7.6 Limitations and Future Research

The current study has many limitations. One being the constraint the BigPharma environment places on playable actions. Indeed, the game provides many realistic options but limits players' creativity in unethical pathways (Ditum, 2016). Though in one respect, this is a good way of steering the player's interaction with the virtual environment into rational and realistic scenarios and actions. However, it may also be considered hindering to the players' ability to develop novel and unforeseeable ways of cheating the PSC. To address this limitation, the authors have floated the idea of using Unity (a game engine) to develop a novel base for this serious game (See Figure 7.3). A previous version of the game shown in Figure 7.3 can be played at-

https://play.unity.com/mg/other/pharmaceuticals.

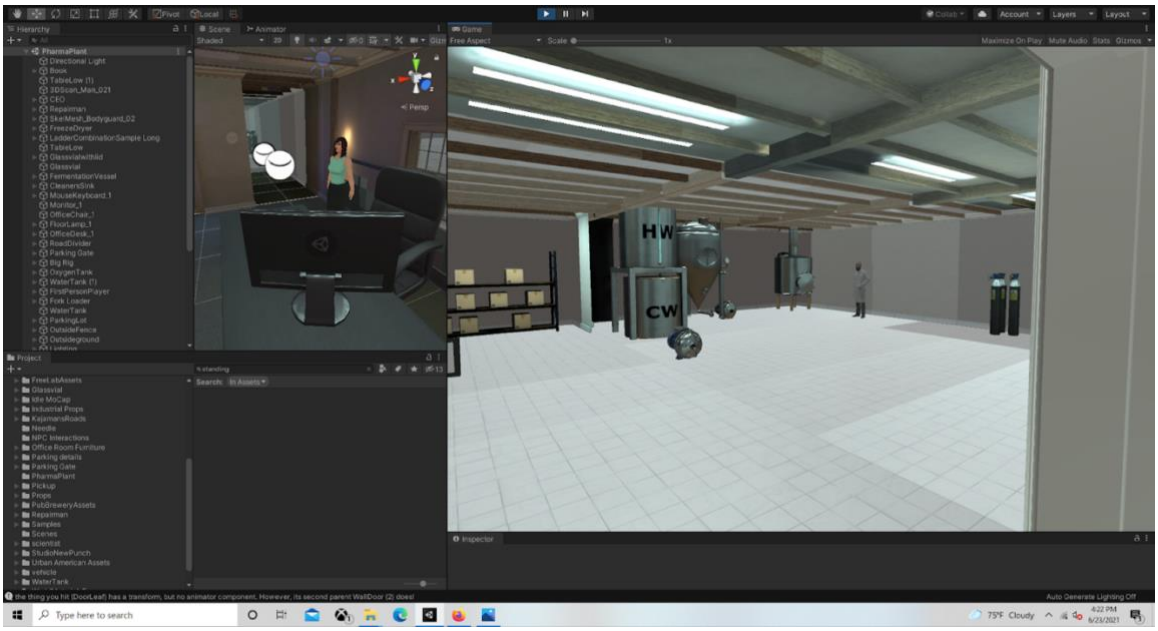

Figure 7.3 Representative scene from investigators novel series game development. Performed in Unity.

Additionally, the study possessed a small sample size. Rendering statistical approaches insignificant. Future research will need to scale the study. It is thought that targeting online BigPharma game forums may be successful in achieving this. Indeed, targeting this audience would result in players who are already familiar with the game mechanics of BigPharma, and such players could participate remotely. Further, it is thought that holding online tournaments which players must pay to enter with entry fees going into a pool for rewards may increase participation as pools can grow increasingly large. However, there may be legal hurdles in developing such a system (GS, 2021). Further play order effects were not explored. Future research should swap the order of quality and profit motives. Despite these limitations, the study provided results reflective of results seen in the DQS as well as results that align with current theory and literature.

7.7 Conclusions

The above study sought to repeat the experiment described in Chapter 6 under competition and non-zero probability of loss constraints. It was thought that under these constraints, players would shy away from high-risk unethical decisions. The observations presented above lend themselves to this idea. Indeed, when comparing the unethical management-level actions taken by players in a non-tournament environment (Chapter 6) to a tournament setting, we see a decrease in attention-drawing activities such as price hiking and selling unapproved drugs. On the other hand, we see an increase in actions that are considered more difficult to detect, such as selling sub-potent drugs or cheap/unapproved materials. Furthermore, when comparing these results to those seen in Chapter 6, players tend to form in-game strategies that they stick to. Suggesting players may form habits in virtual environments. Though this study is limited in sample size, it does align well with the limited amount of literature available.

CHAPTER 8. DOES EVERY PLAYER HAVE A PRICE? THE EFFECTS OF PAYOFFS ON IN-GAME DECISION-MAKING

8.1 Introduction

As presented in Chapter 3, games often consist of a series of rewards and penalties (see Figure 3.5). Further, the magnitude of these rewards and penalties may alter the way players play. For example, the popular board game- Monopoly. It is a well-known aspect of this game that most players want to own Boardwalk (an in-game property) (Barringer, 2015; Monopoly Players, 2019; News, 2008). This (though possibly for other intrinsic reasons for some players) is because the price to rent (price paid to the owner by players who are unfortunate enough to land on the property) this property can be large compared to other properties (Monopoly Players, 2019). Boardwalks' high rent rewards the player who owns it in a way other property do not and motivates players to purchase it. Thereby, alternating the gameplay. Imagine Monopoly without Boardwalk's temptation. Then it may be possible for players to see more optimal strategies such as buying Illinois Avenue, Kentucky Avenue, Indiana Avenue, or Pennsylvania Railroad, which are landed on more frequently than Boardwalk (Collins, 1997; Stewart, 1996). In Chapters 6 and 7, a novel series gaming system was presented along with a series of results. In these games players were presented with a series of worker-level decisions. In order to complete these tasks specific costs in the form of in-game currency were required. In this way, costs acted as penalties for doing the right thing (e.g., testing the water system for microbes). This chapter asks if the magnitude of these penalties altered players' decisions in a similar fashion as

Boardwalk alters gameplay for many in Monopoly. The hypothesis tested is that with increased cost to act ethically, the number of unethical worker-level decisions will increase.

8.2 Methods

To test if increasing the cost to act ethically will result in an increased number of unethical worker-level decisions, the same setup is used as in Chapter 6. That is, players played Prompt 1, 2, and 3 games in a non-tournament environment. Further, the same players (Players A, B, C, and D) participated in this study. When examining the worker-level decisions made in Chapter 6 by these players, Player C was the only unethical decision-maker. In addition, to being the only unethical worker-level decision-maker, Player C was by far the most profitable. Therefore, it did not seem as if Player C was basing their decision on affordability. Indeed, they could have covered the cost for their worker tasks and most other players' worker tasks. Given this and players' time constraints, it was decided only to explore increasing the costs per task. Hence, the purpose of this gaming experiment (Prompt 1.0.2) is to explore the effects (if any) of increasing payoff magnitudes on ethical decision-making.

8.3 How much should tasks be increased?

The monetary costs for worker tasks in the Controls, Prompts 1, 2, and 3 were based on investigator gameplay and assumed that each player would earn roughly $100,000 in-game. This assumption provided a starting point because players' average earning ability was unknown. At the time of this study's design, investigators had collected data from several Control, Prompt 1, and Prompt 2 gaming sessions. It was decided that the cost adjustment would be based on the overall average in-game earnings from the data collected

at the time of design in Controls, Prompt 1, and 2 games (See Table 8.1). Where a 10, 100, and 1000-fold increase was under consideration.

Table 8.1 Collected in-game revenue data per game as of March 11th, 2021, 3:06pm. Negative values are highlighted in red. Positive values are highlighted in green. Significant outliers are highlighted in blue.

Source	In-game Revenue ($)
Prompt 1	-50328
Prompt 1	162684
Prompt 1	3862998
Prompt 1	281378
Prompt.2	4259050
Prompt.2	328159
Prompt 1 Control	155967
Prompt 1 Control	147618
Prompt 1 Control	172961
Prompt 1 Control	157561
Prompt 1 Control	144420
Prompt 1 Control	176770
Prompt 1 Control	155645
Prompt 1 Control	141948
Prompt 1 Control	173370
Average	684680.0667

*Note both outliers were earned by Player D.

As can be seen from Table 8.1, two data points are significantly higher than the rest. To identify appropriate cost adjustments for the population, these two (highlight in blue) values were omitted from consideration. Table 8.2 summarizes the updated data set and overall, in-game revenue average. After omitting the outliers in Table 8.1 the average in-game revenue dropped from $684680 to $165242. Note that this is only $65,000 more than the previous assumption.

Table 8.2 Collected in-game revenue adjusted data per source as of March 11th, 2021, 3:06pm. Negative values are highlighted in red. Positive values are highlighted in green. Significant outliers are highlighted in blue.

Source	In-game Revenue ($)
Prompt 1	-50328
Prompt 1	162684
Prompt 1	281378
Prompt 2	328159
Prompt 1 Control	155967
Prompt 1 Control	147618
Prompt 1 Control	172961
Prompt 1 Control	157561
Prompt 1 Control	144420
Prompt 1 Control	176770
Prompt 1 Control	155645
Prompt 1 Control	141948
Prompt 1 Control	173370
Average	165242.5385

Considering an average in-game revenue of $165242, the increased cost per task was adjusted 10-fold (where a 10, 100, and 1000-fold increase was under-consideration). A 10-fold increase was chosen as opposed to a 100 or 1000-fold increase to mitigate the possibility that unethical decisions would be made solely because the player could not afford otherwise. Table 8.3 summarizes the cost adjustments.

Table 8.3 Summary of cost per task before and after 10-fold adjustment.

Task	Cost per Task ($)	Updated Cost per Task ($)
Task 1	500	5000
Task 2	8000	80000
Task 3	0	10
Task 4	15000	150000
Task 2.1	23000	230000
Task 2.2	1200	12000

8.4 Results

Comparing player's worker-level decisions in prompt 1 (original costs) compared to prompt 1.0.2, it is seen that the occurrences of unethical decisions did not increase but stayed the same (See Figure 8.1). Where choice 3 is unethical, choice 2 is ethical, and choice 1 is an unprompted task. However, the number of players participating in unethical decision-making increased. Interestingly, Player D, who throughout the study performed all tasks ethically, decided against Task 4 under this constraint.

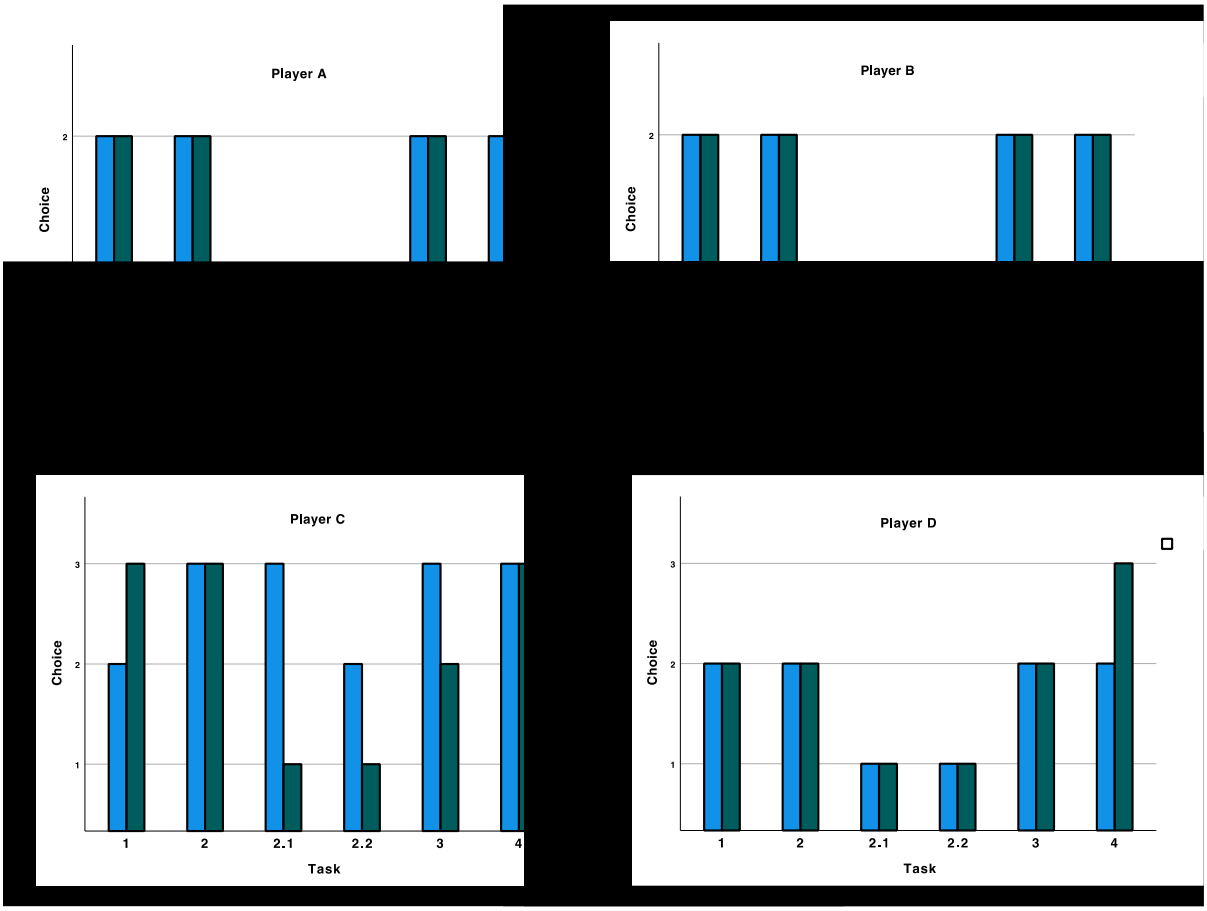

Figure 8.1 Summarizes players' ethical and unethical decision-making per task in prompt 1 (low costs red) and prompt 1.0.2 (high costs blue). Unethical decisions are choice values of 3 and choice value $\leq$ **2** are ethical. Specifically, choice values of 1 are "null" tasks (not presented) and choice values of 2 are ethically completed tasks.

Looking closer at Player D, it is observed that Task 4 was the costliest of Player D's tasks. Player D's decision to act unethically in this task instead of others may suggest that a cost threshold of sorts exists for some individuals. On the other hand, Player A and B continued completing tasks ethically. This may have been because i) their threshold was not reached or ii) these players would do the right thing no matter the costs. This seems to be the opposite of Player C, who continued to act unethically despite the magnitude of

costs. Indeed, Hilbig observed similar actions when examining incentive size on individual's ethical decision-making (Hilbig and Thielmann, 2017). In this study, four types of individuals were identified. First, what the study calls ''corruptible individuals" who cheat more with increasing incentive. It seems Player D may fall into this category. Next, ''small sinners" are those Hilberg states will cheat less as the incentives increase. This type of individual is not observed in this study. However, it may be a result of a small sample size. Hilbig's ''Brazen liars" are those willing to cheat for any non-zero incentive. It seems Player C fits this profile well. Given it is observed that Player C made unethical decisions regardless of the cost (e.g., Player C unethically performed task 3-a zero cost. See Table 8.3 and Table 6.3). Lastly, the Hilbig study identified ''honest individuals," which are those who do not cheat regardless of the incentive (Hilbig and Thielmann, 2017). Potentially Players A and B fit this profile. It is important to note that the above description omits the fact that all players made unethical management-level decisions (See Appendix 5 for more details on players' management frauds). That is, a distinction is being made between the worker and management-level decision-making.

In this study, the effects of costs were strictly considered in worker-level decision-making. Though future work should consider the effects of costs on management level decision-making, the current serious gaming system is not well equipped for this type of study. This is because the current game is designed to reflect (much like reality) not the costs of management-level frauds but the risks of those actions. For example, a player's decision to conceal clinical results is not presented with a performance cost (what it costs to conceal). Instead, the potential increase in sales and warning that the public may one day find out about the unethical decision is presented. Additionally, management-level frauds

were exclusive to the BigPharma COTS gaming environment. Though the game can be modified, the level of modification needed to present players' cost to these actions would be time-consuming. Indeed, building a new basis from Unity, as mentioned in Chapter 7, would be a more favorable option. Though this too will be time-consuming it should be a point for future research

8.5 Conclusion

The above study sought to test the hypothesis that with increased cost to act ethically, the number of unethical worker-level decisions will increase. As presented in the population studied, there is not room to support this hypothesis. Instead, the observations lend support to observations seen by Hilbig (Hilbig and Thielmann, 2017). That is, the current study lends support that there may be four distinct types of individuals. Individuals who will cheat no matter the payoff. Individuals who will never cheat no matter the payoff. Individuals who will cheat less when the incentives increase, and lastly, those who will cheat more with increasing incentives. Hence, this data does not suggest that every player has a price!

CHAPTER 9. A CLOSER LOOK AT QUALITY POINTS. DECIET OR MISUNDERSTANDING AMONGST PLAYERS?

9.1 Introduction

In Chapters 6 and 7, players played through a series of three games, Prompt 1,2, and 3. Prompt 1 players were encouraged to play strictly for-profit by maximizing their in-game revenues. In Prompt 2, players were encouraged to gain all ten quality points (See Appendix 3-BigPharma Quality Rubric). And Prompt 3 players were encouraged to maximize their quality points and profit. Until now, quality points have been described as a rewarding system for players to conduct tasks typically attributed to a high-quality product. For example, cleaning the facility. In this chapter, a closer look at the players' choices regarding quality points is examined.

Quality points were earned through a series of quality attributed tasks (See Appendix 3-Quality Points Rubric). There were 10 possible quality points to be earned. As a group (Player A, B, C, D, T1, and T2) the players did well acquiring quality points. Earning 6.7 points on average in Prompt 2 (collectively both non-tournament and tournament environments) and 6.3 points on average in Prompt 3. Notably, the point average was slightly lower when profit was reintroduced as a motivator in Prompt 3. Though more interestingly, players developed unforeseen ways to conduct the quality tasks. For example, players were intended (and instructed-see Figure 9.1) to clean their entire facility to earn the corresponding quality point.

Figure 9.1 Visual instructions given to players to aid the correct completion of the cleaning quality tasks. Where the imagine on the left depicts a facility before cleaning and the right depicts a cleaned facility. The red circle on the left imagine highlights a dirty area.

However, some players were creative only cleaning the dirty areas or just the walls of their virtual facility (See Figure 9.2).

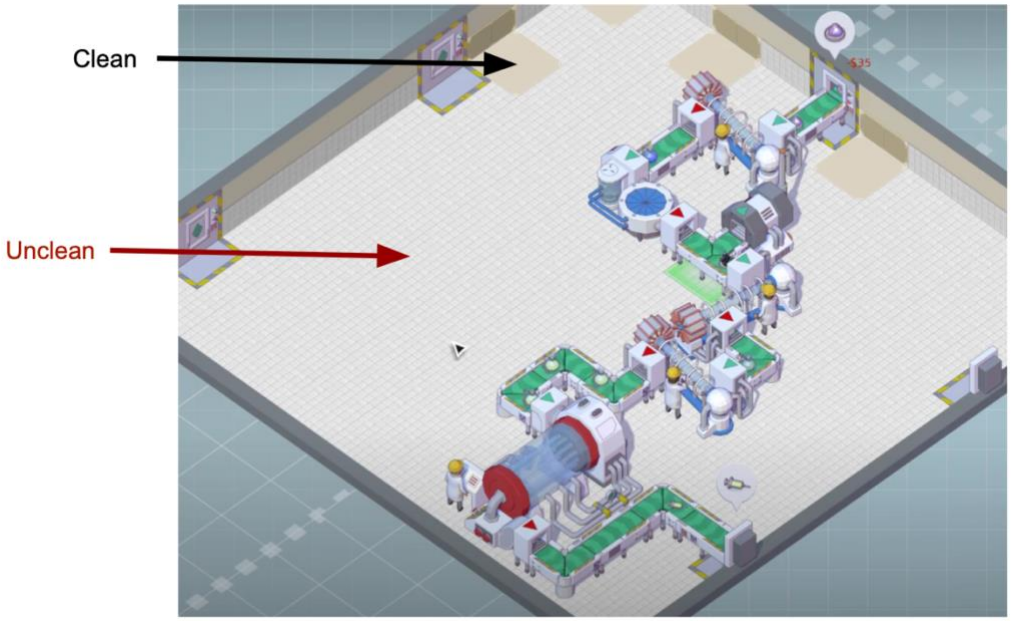

Figure 9.2 Screenshot of a player's creative "solution" to cleaning. The black arrow points to the area which the player cleaned (darker shaded area). While the red arrow points to the lighter shaded unclean area.

Furthermore, during the studies presented in Chapters 6 and 7, consistent behavior among players emerged (See Tables 9.1 and 9.2). While attempting to gain analysis-related quality points (see Figure 9.3), players often misused the in-game analyzer. Resulting in only one player (Player B) throughout the study earning these two points (See Tables 9.1 and 9.2).

Table 9.1 Summary of quality points earned by each player per task in Prompt 2. Both non-tournament (Player A, B, C, and D) and tournament (Player T1 and T2) data are provided.

Task	A	B	C	D	T1	T2
Cleaning Your Facility	1	1	1	0	0	0
Maximizing Drug Concentrations	2	0	0	2	2	2
Analyze your Drugs	0	0	0	0	0	0
Analyze your Ingredients	0	0	0	0	0	0
Clinically testing your Drugs	2	2	2	2	2	2
Implementing Tracing	1	1	1	1	1	1
Taking Inventory	1	1	1	1	1	1
Continuous Improvement	1	1	1	1	0	1
Total	8	6	6	7	6	7

Table 9.2 Summary of quality points earned by each player per task in Prompt 3. Both non-tournament (Player A, B, C, and D) and tournament (Player T1 and T2) data are provided.

Task	A	B	C	D	T1	T2
Cleaning Your Facility	0	1	0	0	0	0
Maximizing Drug Concentrations	0	0	2	2	2	2
Analyze your Drugs	0	1	0	0	0	0
Analyze your Ingredients	0	1	0	0	0	0
Clinically testing your Drugs	2	2	2	2	2	2
Implementing Tracing	1	1	1	1	1	1
Taking Inventory	0	1	1	1	1	1
Continuous Improvement	0	1	1	1	0	1
Total	3	8	7	7	6	7

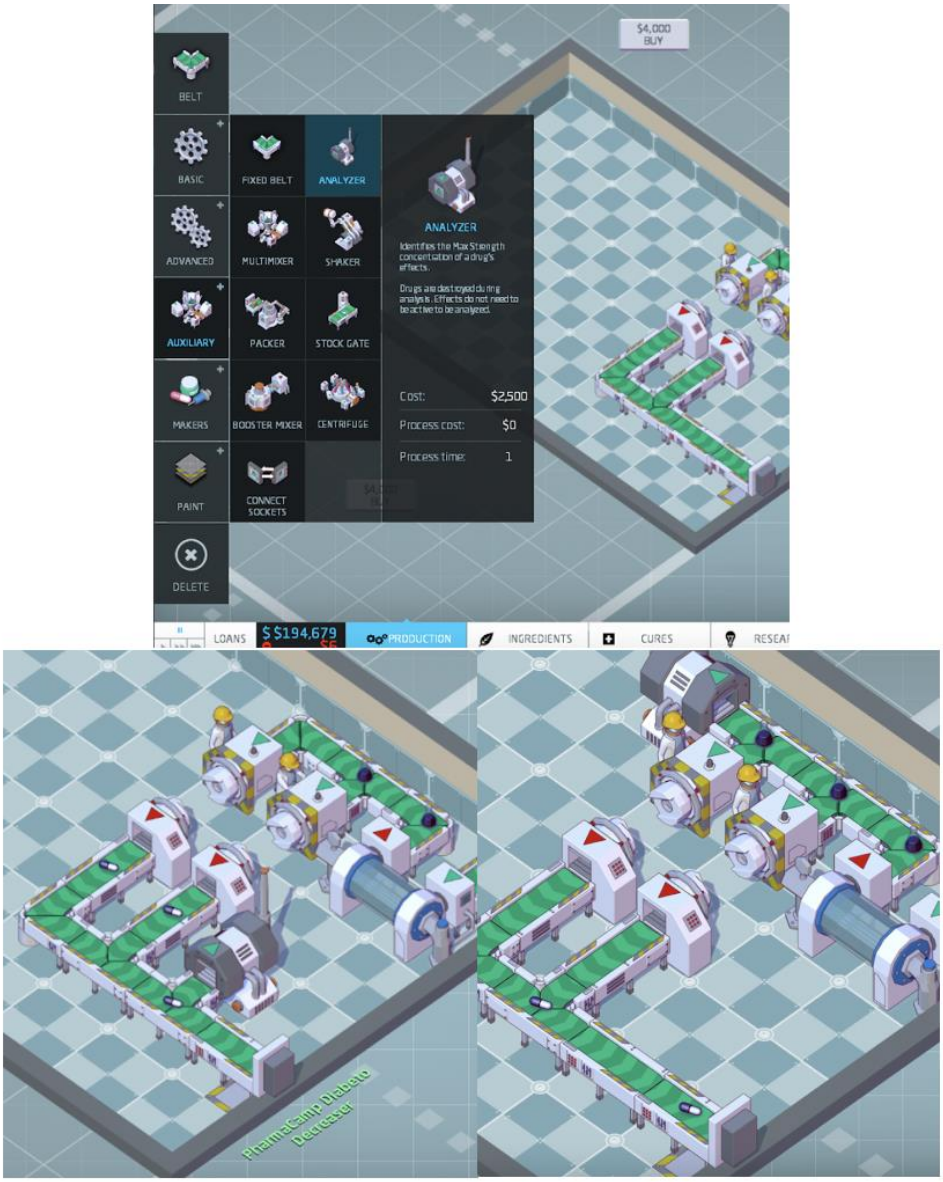

Figure 9.3 Visual depiction of in-game analysis (product bottom left, ingredient bottom right) via the analyzer tool (top).

The intent was for players to analyze both their drug and ingredients for the entirety of their gaming session. However, most players analyzed their in-game drug and ingredients only for a short time before stopping. Others acted similarly but only analyzed their in-game drug or ingredients. To this point, it remains unclear whether players consciously acted defiantly or if this behavior stemmed from miscommunication based on

the rubric wording. However, this is a generous question for two of the players given their backgrounds are in pharmacology. On this note, the one player who did gained the analyzer points did not possess such a background. Nevertheless, the question remains, and the purpose of this study is to explore this question by testing the hypothesis that players will follow analyzer guidelines when presented with an amended rubric. In the next section, the specifics of the amendments are laid out.

9.2 An Updated Quality Rubric

As mentioned above, up to this point in the project, it remains unclear if players' un-intended behavior concerning analysis quality tasks were intentionally deceitful or stem from a misunderstanding of the rubric's language. To investigate this behavior and test the hypothesis that players will follow analyzer guidelines when presented with an amended rubric, an updated rubric needed to be created. Specifically, the two tasks of interest (analyzing drugs and analyzing ingredients) were updated while the rest remained the same. The first update was to analyzing drugs. The original rubric read as follows:

"Analyze your Drugs - 1 QP

Use the analyzer on all drugs produced to gain this QP. Click here for a step-by-step example."

This was replaced with

"**Analyze your Drug <u>Product</u> - 1 QP**

Use the analyzer on **<u>your</u>** drug **<u>product (processed-syringe) throughout the game to gain this QP. This should be done before selling your drug, while selling your drug, and continue after the analyzer produces a result. Consider the analyzer a process analytical technology that the FDA requires you to use all the time</u>**. **<u>Click here</u>** for an example."

The second update was to the analyzing ingredient task. The original rubric reads as follows:

“Analyze your Ingredients - 1 QP

Use the analyzer on all drugs produced to gain this QP. Click here for a step-by-step example.”

This was replaced with

“Analyze your Ingredients - 1 QP

Use the analyzer on all drug **ingredients throughout the game to gain this QP. This should be done before selling your drug, while selling your drug, and continue after the analyzer produces a result. Consider the analyzer a process analytical technology that the FDA requires you to use all the time. Click here** for an example.”

With this update, the changes to the rubric were complete (see the wholly amended rubric in Appendix 6). The following section briefly describes the methods of this study.

9.3 Methods

Players T1 and T2 from the tournament play participated in this study. In this way, players' previous actions could be compared with the current data. Given that the goal of this study was not focused on the relationship between profit on behavior, players were only asked to play the Prompt 2 game. In this way, players were strictly motivated by earning quality points. All technical aspects of the study remained the same as in Chapter 7, excluding the constraints of competition amongst each other. Players played at the tournament location (UK's esports lounge). Players played uninterrupted once beginning and were told at the beginning of the game that changes had been made to the supplement

material. Players were not informed of the specific change, and it was left up to them to find. The results of this study are presented next.

9.4 Results

Table 9.3 summarizes Player T1 and T2's results from the tournament (which players were presented the original rubric) and current game – Prompt 1.2.1 (which presented the amended rubric to players). Playing under the original rubric, both players did not earn their quality points for analyzing their respective drug or ingredients. Opposed to when players are presented with the amended rubric. In addition to players earning the analyzer points, the players also gained the cleaning facility point.

Table 9.3 Summary of players quality points earned when playing under the original rubric versus the amended-updated- rubric.

		Original Rubric		Amended Rubric	
Task	Quality Points Possible	Player T1	Player T2	Player T1	Player T2
Cleaning Your Facility	1	0	0	1	1
Maximizing Drug Concentrations	2	2	2	2	2
Analyze your Drug	1	0	0	1	1
Analyze your Ingredients	1	0	0	1	1
Clinically testing your Drugs	2	2	2	2	2
Implementing Tracing	1	1	1	1	1
Taking Inventory	1	1	1	1	1
Continuous Improvement	1	0	1	1	1
Total	10	6	7	10	10

Previously players had only cleaned specific areas or not cleaned at all in their virtual processing plant. This was not considered sufficient for earning the cleaning quality point as the instructions showed players to clean the plant in its entirety (See Table 9.3 and Figure 9.3). The players opted to switch this behavior in addition to the analyzer tasks playing under the updated rubric (See Table 9.3). This may lend evidence that the players

experienced investigation bias. Given players were told that only a slight change in the supplement information was done (though not told what that change was), the players may have felt pressured to adhere to the supplement information (aka the rubric and instructions) more than in Prompt 2 (original rubric presented). Regardless of this, the players did perform the analyzer tasks correctly under the amended rubric. Given that players were also informed to follow the rubric in the Prompt 2 tournament game, one could assert that the players may have possessed a similar focus or pressure towards following the original rubric, but they seemingly did not (they did not follow the rubric). From this light, the amended rubric made clearer the task at hand such that the player could follow the instructions correctly. However, the study is difficult to draw conclusions on in this regard due to its small sample size and potential bias. Further, the players' non-competition environment for this study may have allowed them to focus less on profit in prompt 2 and more on quality. However, this is not likely the case because nearly all players in the non-tournament environment did not adhere to the task's intended requests either.

Lastly, Table 9.4 summarizes the worker-level decisions players made while playing under the amended rubric.

Table 9.4 Player T1 and T2's worker-level decisions. Ethical decisions are in green, unethical in red and unprompted are in blue.

	Player T2	Player T1
Task 1	(+)	(+)
Task 2	(+)	(-)
Task 3	(+)	(+)
Task 4	(+)	(+)
Task 2.2	null	null
Task 2.3	null	null

From Table 9.4, it is observed that Player T2 completed all worker-level decisions ethically. While Player T1 completed all worker-level decisions ethically except for Task 2. Both Players had previously made all ethical decisions under the original rubric (and under competition, i.e., tournament environment). Taking a closer look at Player T1's strategy through the ethical timetables (see Appendix 6-Ethical Timetables), we see that the player was in debt at the time of Task 2 (see Figure 9.4).

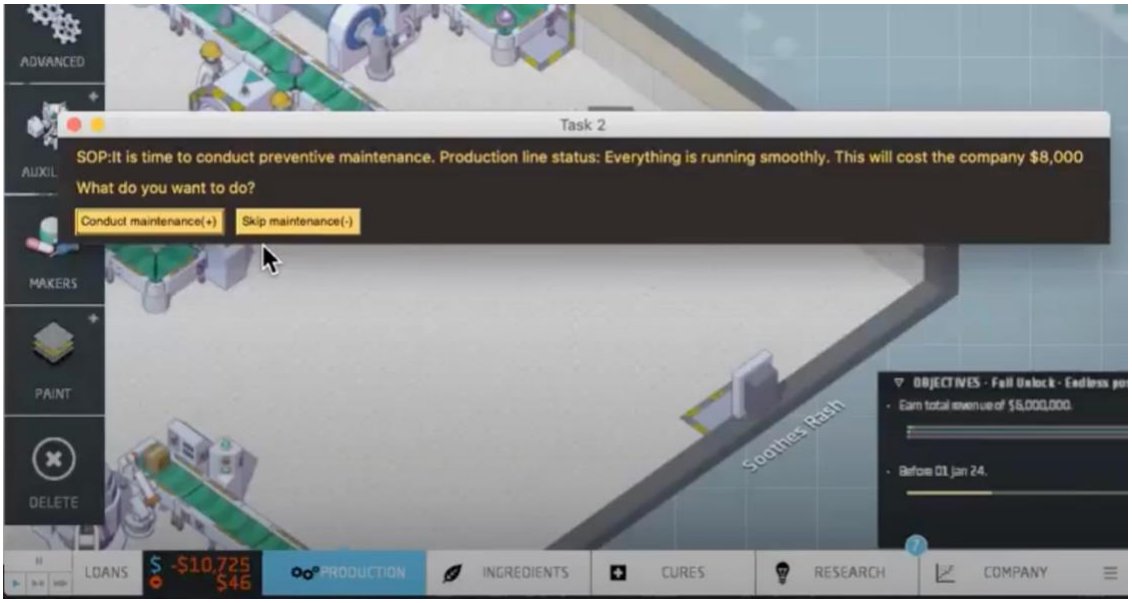

Figure 9.4 Screenshot of Player T1's virtual environment at time of Task 2 decision. Note the player was ten thousand dollars in debt.

Player T1's unethical decision while in debt aligns well with the results seen in Chapter 6 from Player A. Both players' actions are well exampled by the Fraud Triangle Theory, which suggests debt is a driving force for fraudulent behavior (AGA, 2015). Additionally, it should be noted from the players' video that the player suffered debt due to the cost demands associated with the analyzer tasks. This behavior may suggest that when players are put under increasingly stricter quality guidelines (specifically financially burdensome tasks), players may find other ways to "make up" the costs in unethical ways even when rewarded for quality.

9.5 Conclusion

Players' unexpected behavior in regard to completing analysis-related quality tasks was investigated. As it was unknown if players intentionally acted deceitfully or if there was a miscommunication due to the language of the rubric. In this study, an updated quality

rubric was provided to players. Players T1 and T2 played through the quality motivated game (Prompt 2) using the updated rubric. It was found that players did perform the analysis tasks correctly under the updated rubric. However, due to the limitations of the study that is a small sample size and potential pressures, it is difficult to assert the change was due to the updated rubric. Nevertheless, the data suggest that when players are put under increasingly stricter quality guidelines (specifically financially burdensome tasks), players may find other (potentially unethical) ways to make up for the costs even when they are rewarded for quality.

APPENDICES

APPENDIX 1. PYTHON SOURCE CODE

PROMPT 1

To install GUI run:

pip install pysimplegui or pip3 install pysimplegui

#https://pysimplegui.readthedocs.io/en/latest/

```
import PySimpleGUI as sg
import time
import tkinter as Tk
root =Tk.Tk()
root.overrideredirect()
min = 3.0; # number of minutes i want the code to wait to execute
sec = min*60; #convert to seconds
time.sleep(sec) #wait to execute code for "sec" seconds
sg.theme('DarkAmber')   # Add a touch of color
# All the stuff inside your window.
layout = [  [sg.Text('SOP: Thoroughly clean water tank and conduct microbial testing. This will cost the company $500',font='14')],
        [sg.Text('What do you want to do?',font='14')],
        #[sg.Text('Enter something on Row 2'), sg.InputText()],
```

```
        [sg.Button('Clean(+)'), sg.Button('Decline (-)'),sg.Button('Ask co-worker to
do it.')] ]
#Penalty variable n
n=0;
# Create the Window
window = sg.Window('Task 1', layout)
# Event Loop to process "events" and get the "values" of the inputs
while True:
   event, values = window.read()
   if event == sg.WIN_CLOSED or event == 'Decline (-)': # if user closes window or
clicks cancel
      ss1=0
      ss2=0
      print('Task 1: Declined')
      break
   if event =='Clean(+)' :
      ss1=0
      ss2=0
      print("Task 1 Clean")
      break
```

```
    if event =='Ask co-worker to do it.' :
        ss1=1
        ss2=1
        print("Task 1 Ask co-worker to do it.")
        break
window.close()
if ss1== 1 :
    layouts = [  [sg.Text('Who do you wish to ask?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Steven: Techican I'), sg.Button('Miranda: Plant Engineer')] ]
    window = sg.Window('Task 1', layouts)
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Steven: Techican I': # if user closes
window or clicks cancel
                print('Tech')
                break
        if event =='Miranda: Plant Engineer' :
                print('engineer')
                break
```

```
window.close()
if ss2==1 :
    mins = 15.0-min; # number of minutes i want the code to wait to execute
    secs = mins*60; #convert to seconds
    time.sleep(secs) #wait to execute code for "sec" seconds
    layout = [  [sg.Text('You asked your co-worker',font='14')],
          [sg.Text('Do you want to see if your co-worker did it?',font='14')],
         #[sg.Text('Enter something on Row 2'), sg.InputText()],
         [sg.Button('Check.(+)'), sg.Button('Trust coworker did it.(-)')] ]
    window = sg.Window('Task 1.1', layout)
            # Event Loop to process "events" and get the "values" of the inputs
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Trust coworker did it.(-)': # if user
closes window or clicks cancel
            print("Task 1.1 :Trusted coworker")
            break
        if event =='Check.(+)' :
            print("Task 1.1: Check")
            break
```

```
   window.close()
min2 = 24.0-min; # number of minutes i want the code to wait to execute
sec2 = min2*60; #convert to seconds
time.sleep(sec2) #wait to execute code for "sec" seconds
layout2 = [  [sg.Text('SOP:It is time to conduct preventive maintenance. Production line status: Everything is running smoothly. This will cost the company $8,000',font='14')],
        [sg.Text('What do you want to do?',font='14')],
        #[sg.Text('Enter something on Row 2'), sg.InputText()],
        [sg.Button('Conduct maintenance(+)'), sg.Button('Skip maintenance(-)')] ]
# Create the Window
window = sg.Window('Task 2', layout2)
# Event Loop to process "events" and get the "values" of the inputs
while True:
   event, values = window.read()
   if event == sg.WIN_CLOSED or event == 'Skip maintenance(-)': # if user closes window or clicks cancel
      print('Task 2 Skip')
      HC=1
      SL=0
```

```
        break
    if event =='Conduct maintenance(+)' :
        print('Task 2 Conduct')
        HC=0
        SL=0
        break
window.close()
"Task 3"
min3 = 6.0; # number of minutes i want the code to wait to execute
sec3 = min3*60; #convert to seconds
time.sleep(sec3) #wait to execute code for "sec" seconds
layout3 = [  [sg.Text("SOP: It's time to do microbial testing.",font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Test(+)'), sg.Button('Skip(-)')] ]
# Create the Window
window = sg.Window('Task 3', layout3)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
```

```
    if event == sg.WIN_CLOSED or event == 'Test(+)': # if user closes window or
clicks cancel
        print('Task 3 Test')
        break
    if event =='Skip(-)' :
        k=-2
        n=n+k
        print('Task 3 Skip')
        break
window.close()
"Task 4"
min4 = 6.0; # number of minutes i want the code to wait to execute
sec4 = min4*60; #convert to seconds
time.sleep(sec4) #wait to execute code for "sec" seconds
layout4 = [  [sg.Text("Your quality engineer has found contaminants in products.
They recommend the last 2 batches of products be thrown out. This will cost the
company $15,000",font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
```

```
        [sg.Button('Sell batches anyway (-)'), sg.Button('Sell batches by mixing
contaminated products within good batches'),sg.Button('Throw out batches(+)')] ]
# Create the Window
window = sg.Window('Task 4', layout4)
# Event Loop to process "events" and get the "values" of the inputs
while True:
   event, values = window.read()
   if event == sg.WIN_CLOSED or event == 'Sell batches anyway (-)': # if user closes
window or clicks cancel
      print('Task 4 Sell batches anyway (-)')
      break
   if event =='Sell batches by mixing contaminated products within good batches' :
      print('Task 4 Sell batches by mixing contaminated products within good
batches')
      break
   if event =='Throw out batches(+)' :
      print('Task 4 Throw out batches(+)')
      break
window.close()
if HC== 1 :
```

```
    minHC = 6.0; # number of minutes i want the code to wait to execute
    secHC = minHC*60; #convert to seconds
    time.sleep(secHC) #wait to execute code for "sec" seconds
    layouts2 = [  [sg.Text('Your quality engineer has identified rust particles in products. They suggest throwing out the last 4 batches of product out and shutting down the lines to inspect for rust. This will cost the company $23,000.',font='14')],
          #[sg.Text('Enter something on Row 2'), sg.InputText()],
          [sg.Button('Inspect(+)'), sg.Button('Keep going'), sg.Button('Keep going and fire quality engineer(-)')] ]
    window = sg.Window('Task HC', layouts2)
    while True:
       event, values = window.read()
       if event == sg.WIN_CLOSED or event == 'Inspect(+)': # if user closes window or clicks cancel
             SL=1
             print('HC: Inspect(+)')
             break
       if event =='Keep going' :
             SL=1
             print('HC : Keep going')
```

```
            break
        if event =='Keep going and fire quality engineer(-)' :
            SL=0
            print('HC : Keep going and fire quality engineer(-)')
            break
window.close()
if SL== 1 :
    minSL = 9.0; # number of minutes i want the code to wait to execute
    secSL = minHC*60; #convert to seconds
    time.sleep(secSL) #wait to execute code for "sec" seconds
    layouts3 = [  [sg.Text('Your quality engineer has detected issues with record keeping. They suggest everyone be retrained. This will cost the company $1200.',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Retrain (+)'), sg.Button('Ignore'), sg.Button('Ignore and fire quality engineer(-)')] ]
    window = sg.Window('Task SL', layouts3)
    while True:
        event, values = window.read()
```

```
    if event == sg.WIN_CLOSED or event == 'Retrain (+)': # if user closes window
or clicks cancel
            SL=0
            print('SL: Retrain (+)')
            break
    if event =='Ignore' :
            SL=0
            print('SL : Ignore')
            break
    if event =='Ignore and fire quality engineer(-)' :
            SL=1
            print('SL : Ignore and fire quality engineer(-)')
            break
window.close()
```

PROMPT 2

```
import PySimpleGUI as sg
import time
import tkinter as Tk

root =Tk.Tk()
```

```
root.overrideredirect()
min = 5.0; # number of minutes i want the code to wait to execute
sec = min*60; #convert to seconds
time.sleep(sec) #wait to execute code for "sec" seconds


sg.theme('DarkAmber')   # Add a touch of color
# All the stuff inside your window.
layout = [  [sg.Text('SOP: Thoroughly clean water tank and conduct microbial testing.
This will cost the company $500',font='14')],
          [sg.Text('What do you want to do?',font='14')],
          #[sg.Text('Enter something on Row 2'), sg.InputText()],
          [sg.Button('Clean(+)'), sg.Button('Decline (-)'),sg.Button('Ask co-worker to do
it.')] ]


#Penalty variable n
n=0;


# Create the Window
window = sg.Window('Task 1', layout)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
```

```
    if event == sg.WIN_CLOSED or event == 'Decline (-)': # if user closes window or
clicks cancel
        ss1=0
        ss2=0
        print('Task 1: Declined')
        break
    if event =='Clean(+)' :
        ss1=0
        ss2=0
        print("Task 1 Clean")
        break
    if event =='Ask co-worker to do it.' :
        ss1=1
        ss2=1
        print("Task 1 Ask co-worker to do it.")
        break
window.close()


if ss1== 1 :
    layouts = [  [sg.Text('Who do you wish to ask?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Steven: Techican I'), sg.Button('Miranda: Plant Engineer')] ]
    window = sg.Window('Task 1', layouts)
```

```
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Steven: Techican I': # if user closes
window or clicks cancel
                print('Tech')
                break
        if event =='Miranda: Plant Engineer' :
                print('engineer')
                break
window.close()


if ss2==1 :
    mins = 25.0-min; # number of minutes i want the code to wait to execute
    secs = mins*60; #convert to seconds
    time.sleep(secs) #wait to execute code for "sec" seconds
    layout = [  [sg.Text('You asked your co-worker',font='14')],
            [sg.Text('Do you want to see if your co-worker did it?',font='14')],
           #[sg.Text('Enter something on Row 2'), sg.InputText()],
           [sg.Button('Check.(+)'), sg.Button('Trust coworker did it.(-)')] ]
    window = sg.Window('Task 1.1', layout)
              # Event Loop to process "events" and get the "values" of the inputs
    while True:
        event, values = window.read()
```

```
        if event == sg.WIN_CLOSED or event == 'Trust coworker did it.(-)': # if user closes
window or clicks cancel
                print("Task 1.1 :Trusted coworker")
                break
        if event =='Check.(+)' :
                print("Task 1.1: Check")
                break
    window.close()


min2 = 40.0-min; # number of minutes i want the code to wait to execute
sec2 = min2*60; #convert to seconds
time.sleep(sec2) #wait to execute code for "sec" seconds


layout2 = [  [sg.Text('SOP:It is time to conduct preventive maintenance. Production line
status: Everything is running smoothly. This will cost the company $8,000',font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Conduct maintenance(+)'), sg.Button('Skip maintenance(-)')] ]


# Create the Window
window = sg.Window('Task 2', layout2)
# Event Loop to process "events" and get the "values" of the inputs
while True:
```

```
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Skip maintenance(-)': # if user closes
window or clicks cancel
        print('Task 2 Skip')
        HC=1
        SL=0
        break
    if event =='Conduct maintenance(+)' :
        print('Task 2 Conduct')
        HC=0
        SL=0
        break

window.close()

"Task 3"
min3 = 10.0; # number of minutes i want the code to wait to execute
sec3 = min3*60; #convert to seconds
time.sleep(sec3) #wait to execute code for "sec" seconds

layout3 = [  [sg.Text("SOP: It's time to do microbial testing.",font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
```

```
            [sg.Button('Test(+)'), sg.Button('Skip(-)')] ]


# Create the Window
window = sg.Window('Task 3', layout3)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Test(+)': # if user closes window or clicks
cancel
        print('Task 3 Test')
        break
    if event =='Skip(-)' :
        k=-2
        n=n+k
        print('Task 3 Skip')
        break


window.close()


"Task 4"
min4 = 10.0; # number of minutes i want the code to wait to execute
sec4 = min4*60; #convert to seconds
time.sleep(sec4) #wait to execute code for "sec" seconds
```

```
layout4 = [  [sg.Text("Your quality engineer has found contaminants in products. They recommend the last 2 batches of products be thrown out. This will cost the company $15,000",font='14')],
        [sg.Text('What do you want to do?',font='14')],
        #[sg.Text('Enter something on Row 2'), sg.InputText()],
        [sg.Button('Sell batches anyway (-)'), sg.Button('Sell batches by mixing contaminated products within good batches'),sg.Button('Throw out batches(+)')] ]

# Create the Window
window = sg.Window('Task 4', layout4)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Sell batches anyway (-)': # if user closes window or clicks cancel
        print('Task 4 Sell batches anyway (-)')
        break
    if event =='Sell batches by mixing contaminated products within good batches' :
        print('Task 4 Sell batches by mixing contaminated products within good batches')
        break
    if event =='Throw out batches(+)' :
        print('Task 4 Throw out batches(+)')
```

```
        break


window.close()


if HC== 1 :
    minHC = 10.0; # number of minutes i want the code to wait to execute
    secHC = minHC*60; #convert to seconds
    time.sleep(secHC) #wait to execute code for "sec" seconds



    layouts2 = [  [sg.Text('Your quality engineer has identified rust particles in products. They suggest throwing out the last 4 batches of product out and shutting down the lines to inspect for rust. This will cost the company $23,000.',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Inspect(+)'), sg.Button('Keep going'), sg.Button('Keep going and fire quality engineer(-)')] ]
    window = sg.Window('Task HC', layouts2)
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Inspect(+)': # if user closes window or clicks cancel
                SL=1
                print('HC: Inspect(+)')
```

```
            break
        if event =='Keep going' :
            SL=1
            print('HC : Keep going')
            break
        if event =='Keep going and fire quality engineer(-)' :
            SL=0
            print('HC : Keep going and fire quality engineer(-)')
            break
window.close()


if SL== 1 :
    minSL = 15.0; # number of minutes i want the code to wait to execute
    secSL = minHC*60; #convert to seconds
    time.sleep(secSL) #wait to execute code for "sec" seconds
    layouts3 = [  [sg.Text('Your quality engineer has detected issues with record keeping.
They suggest everyone be retrained. This will cost the company $1200.',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Retrain (+)'), sg.Button('Ignore'), sg.Button('Ignore and fire quality
engineer(-)')] ]
    window = sg.Window('Task SL', layouts3)
    while True:
        event, values = window.read()
```

```
    if event == sg.WIN_CLOSED or event == 'Retrain (+)': # if user closes window or
clicks cancel
            SL=0
            print('SL: Retrain (+)')
            break
    if event =='Ignore' :
            SL=0
            print('SL : Ignore')
            break
    if event =='Ignore and fire quality engineer(-)' :
            SL=1
            print('SL : Ignore and fire quality engineer(-)')
            break
window.close()
```

PROMPT 3

```
import PySimpleGUI as sg
import time
import tkinter as Tk

root =Tk.Tk()
root.overrideredirect()
min = 5.0; # number of minutes i want the code to wait to execute
```

```
sec = min*60; #convert to seconds
time.sleep(sec) #wait to execute code for "sec" seconds


sg.theme('DarkAmber')   # Add a touch of color
# All the stuff inside your window.
layout = [  [sg.Text('SOP: Thoroughly clean water tank and conduct microbial testing.
This will cost the company $500',font='14')],
          [sg.Text('What do you want to do?',font='14')],
          #[sg.Text('Enter something on Row 2'), sg.InputText()],
          [sg.Button('Clean(+)'), sg.Button('Decline (-)'),sg.Button('Ask co-worker to do
it.')] ]


#Penalty variable n
n=0;


# Create the Window
window = sg.Window('Task 1', layout)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Decline (-)': # if user closes window or
clicks cancel
        ss1=0
```

```
        ss2=0
        print('Task 1: Declined')
        break
    if event =='Clean(+)' :
        ss1=0
        ss2=0
        print("Task 1 Clean")
        break
    if event =='Ask co-worker to do it.' :
        ss1=1
        ss2=1
        print("Task 1 Ask co-worker to do it.")
        break
window.close()


if ss1== 1 :
    layouts = [  [sg.Text('Who do you wish to ask?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Steven: Techican I'), sg.Button('Miranda: Plant Engineer')] ]
    window = sg.Window('Task 1', layouts)
    while True:
        event, values = window.read()
```

```
        if event == sg.WIN_CLOSED or event == 'Steven: Techican I': # if user closes
window or clicks cancel
                print('Tech')
                break
        if event =='Miranda: Plant Engineer' :
                print('engineer')
                break
window.close()


if ss2==1 :
    mins = 25.0-min; # number of minutes i want the code to wait to execute
    secs = mins*60; #convert to seconds
    time.sleep(secs) #wait to execute code for "sec" seconds
    layout = [  [sg.Text('You asked your co-worker',font='14')],
             [sg.Text('Do you want to see if your co-worker did it?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Check.(+)'), sg.Button('Trust coworker did it.(-)')] ]
    window = sg.Window('Task 1.1', layout)
                # Event Loop to process "events" and get the "values" of the inputs
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Trust coworker did it.(-)': # if user closes
window or clicks cancel
```

```
            print("Task 1.1 :Trusted coworker")
            break
        if event =='Check.(+)' :
            print("Task 1.1: Check")
            break
    window.close()
min2 = 40.0-min; # number of minutes i want the code to wait to execute
sec2 = min2*60; #convert to seconds
time.sleep(sec2) #wait to execute code for "sec" seconds

layout2 = [  [sg.Text('SOP:It is time to conduct preventive maintenance. Production line
status: Everything is running smoothly. This will cost the company $8,000',font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Conduct maintenance(+)'), sg.Button('Skip maintenance(-)')] ]

# Create the Window
window = sg.Window('Task 2', layout2)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Skip maintenance(-)': # if user closes
window or clicks cancel
```

```
        print('Task 2 Skip')
        HC=1
        SL=0
        break
    if event =='Conduct maintenance(+)' :
        print('Task 2 Conduct')
        HC=0
        SL=0
        break
window.close()


"Task 3"
min3 = 10.0; # number of minutes i want the code to wait to execute
sec3 = min3*60; #convert to seconds
time.sleep(sec3) #wait to execute code for "sec" seconds


layout3 = [  [sg.Text("SOP: It's time to do microbial testing.",font='14')],
            [sg.Text('What do you want to do?',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Test(+)'), sg.Button('Skip(-)')] ]

# Create the Window
window = sg.Window('Task 3', layout3)
```

```
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Test(+)': # if user closes window or clicks
cancel
        print('Task 3 Test')
        break
    if event =='Skip(-)' :
        k=-2
        n=n+k
        print('Task 3 Skip')
        break

window.close()

"Task 4"
min4 = 10.0; # number of minutes i want the code to wait to execute
sec4 = min4*60; #convert to seconds
time.sleep(sec4) #wait to execute code for "sec" seconds

layout4 = [  [sg.Text("Your quality engineer has found contaminants in products. They
recommend the last 2 batches of products be thrown out. This will cost the company
$15,000",font='14')],
```

```
        [sg.Text('What do you want to do?',font='14')],
        #[sg.Text('Enter something on Row 2'), sg.InputText()],
        [sg.Button('Sell batches anyway (-)'), sg.Button('Sell batches by mixing
contaminated products within good batches'),sg.Button('Throw out batches(+)')] ]

# Create the Window
window = sg.Window('Task 4', layout4)
# Event Loop to process "events" and get the "values" of the inputs
while True:
    event, values = window.read()
    if event == sg.WIN_CLOSED or event == 'Sell batches anyway (-)': # if user closes
window or clicks cancel
        print('Task 4 Sell batches anyway (-)')
        break
    if event =='Sell batches by mixing contaminated products within good batches' :
        print('Task 4 Sell batches by mixing contaminated products within good batches')
        break
    if event =='Throw out batches(+)' :
        print('Task 4 Throw out batches(+)')
        break

window.close()
```

```
if HC== 1 :
    minHC = 10.0; # number of minutes i want the code to wait to execute
    secHC = minHC*60; #convert to seconds
    time.sleep(secHC) #wait to execute code for "sec" seconds


    layouts2 = [  [sg.Text('Your quality engineer has identified rust particles in products. They suggest throwing out the last 4 batches of product out and shutting down the lines to inspect for rust. This will cost the company $23,000.',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Inspect(+)'), sg.Button('Keep going'), sg.Button('Keep going and fire quality engineer(-)')] ]
    window = sg.Window('Task HC', layouts2)
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Inspect(+)': # if user closes window or clicks cancel
                SL=1
                print('HC: Inspect(+)')
                break
        if event =='Keep going' :
                SL=1
                print('HC : Keep going')
```

```
            break
        if event =='Keep going and fire quality engineer(-)' :
            SL=0
            print('HC : Keep going and fire quality engineer(-)')
            break
window.close()


if SL== 1 :
    minSL = 15.0; # number of minutes i want the code to wait to execute
    secSL = minHC*60; #convert to seconds
    time.sleep(secSL) #wait to execute code for "sec" seconds
    layouts3 = [  [sg.Text('Your quality engineer has detected issues with record keeping.
They suggest everyone be retrained. This will cost the company $1200.',font='14')],
            #[sg.Text('Enter something on Row 2'), sg.InputText()],
            [sg.Button('Retrain (+)'), sg.Button('Ignore'), sg.Button('Ignore and fire quality
engineer(-)')] ]
    window = sg.Window('Task SL', layouts3)
    while True:
        event, values = window.read()
        if event == sg.WIN_CLOSED or event == 'Retrain (+)': # if user closes window or
clicks cancel
            SL=0
            print('SL: Retrain (+)')
```

```
            break
        if event =='Ignore' :
            SL=0
            print('SL : Ignore')
            break
        if event =='Ignore and fire quality engineer(-)' :
            SL=1
            print('SL : Ignore and fire quality engineer(-)')
            break
window.close()
```

RANDOM GENERATOR

```
import random as rn

#task1=('Clean(+)','Decline (-)','Ask co-worker to do it.')
task1=(0,1,2)
computer_choice1=rn.choice(task1)
print(f"Task 1: {computer_choice1} ")
if computer_choice1==2 :
    #task11=('Trusted coworker','Check')
    task11=(0,1)
    computer_choice11=rn.choice(task11)
```

```
    print(f"Task 1.1: {computer_choice11} ")
else:
    computer_choice11= 9
    print("null")

'Task 2'
#task2=('Conduct maintenance(+)','Skip maintenance(-)')]
task2=(0,1)
computer_choice2=rn.choice(task2)
print(f"Task 2: {computer_choice2} ")

"Task 3"
#task3=('Test(+)','Skip(-)')
task3=(0,1)
computer_choice3=rn.choice(task3)
print(f"Task 3: {computer_choice3} ")

"Task 4"
task4=(1,2,0)
computer_choice4=rn.choice(task4)
#task4=('Sell batches anyway (-)','Sell batches by mixing contaminated products within
good batches','Throw out batches(+)')
print(f"Task 4: {computer_choice4} ")
```

```
if computer_choice2==1 :
    taskhc=('Inspect(+)','Keep going','Keep going and fire quality engineer(-)')
    taskhc=(0,1,2)
    computer_choicehc=rn.choice(taskhc)
    print(computer_choicehc)
else:
    computer_choicehc= 9
    print("null")
if computer_choice2==1 and computer_choicehc==0 or computer_choicehc==1 :
    tasksl=('Retrain (+)','Ignore','Ignore and fire quality engineer(-)')
    tasksl=(0,1,2)
    computer_choicesl=rn.choice(tasksl)
    print(computer_choicesl)
else:
    computer_choicesl= 9
    print("null")
```

APPENDIX 2. SOURCE CODE FOR BIGPHARMA GAME MODIFICATIONS

Each mod folder consisted of six data files. AI data files relate to the in-game AI competitor company difficulty level and special abilities In this study AI's were not altered. The drug names data file relates to changing the drug names. In this study original drug names were replaced with realistic drug names and dosages. This was done to add to the virtual environment's fidelity. The effects data file related to altering the drugs treatment options and effects. In addition, particular processing requirements could be altered within this file as well. For this study a generic carbonic anhydrase inhibitor drug was added. The modinfo file informed the game of the mods name and description. The names-en data file allowed for the addition of realistic drug names in English. The strings-end data file is required to updated the changes made in the other files within the game. This file was used to change the name of the in-game AI competitor's company. Generic company names were used. All other data files were unaltered. In addition to these files an additional folder entitled "MM" is required within the mod folder. Within the MM folder the described data files were copy and pasted. This allowed for the compatibility of the described modifications within the BigPharma malpractice extension package.

EFFECTS FILE ADDITION

```
// Carbonic Anhydrase Inhibitor
{
    "id":"retention",
    "family":"CarbonicAnhydraseInhibitor",
    "level":0,
```

```
        "sensitivity":2100,
        "baseValue":193,
        "boundary":[2,8],
        "helpRate":80

    }
```

MODINFO FILE

```
{
    "modName":"Prompt 1",
    "modDescription":"This mod provides realistic drug names and more."
        }
```

Note “modName” changed respective to prompt.

NAMES-EN SOURCE CODE

```
{
    "order":["firstPart","secondPart","type"],
    "includeSpaces":true,
    "firstPart":[
    "Warfarin",
    "Acetazolamide",
```

"Ziagen",

"WP",

"Xofluza",

"Ketamine",

"Aromatic",

"Remdesivir",

"Ampicillin",

"Cymbalta",

"Triazolam",

"HP",

"Lorsartan",

"Acetazolamide Injectable",

"acetazolamide Injectable",

"Acetazolamide injectable",

"acetazolamide injectable",

"acetazolamide",

"Acetazolamide",

"Melatonin",

"Jencycla",

"Vyvanse",

"Tylenol",

"Zyrtec",

"Ibuprofen",

"Aspirin",

"Humira",

"Enbrel",

"Keytruda",

"Rituxan",

"Abatacept",

"Pertuzumab",

"Ocrelizumab",

"Dasatinib",

"Daratumumab",

"Gardasil",

"Fluticasone",

"Nexium",

"Lantus",

"Celecoxib",

"Insulin",

"Liraglutide"

],

"secondPart":[

"Acid",

"HCl",

"USP 35mg",

"USP 6mg",

"usp 100mg",

"usp 50mg",

"Quick Dissolve",

"USP 500mg",

"USP",

"usp",

"usp 5mg",

"EU 10mg",

"usp 50mg",

"usp 500mg",

"usp 6mg",

"hcl",

"HCL",

"lb",

"Sodium",

"Xalic Acid",

"Fitric Acid",

"QD",

"USP 5mg",

"USP 2mg",

"USP 1mg",

"USP 60mg",

"USP 5mg",

"USP 10mg",

"USP 70mg",

"EU 80mg",

"USP 800mg",

"USP 900mg",

"USP 1000mg"

],

"powders":[

"Powder",

"Dust",

"Precipitate",

"Residue",

"Ash",

"Particles"

],

"crystals":[

"Crystals",

"Concentration",

```
        "Quartz"
],

"solutions":[
        "Juice",
        "Sap",
        "Solution",
        "Oil",
        "Liquid",
        "Extract",
        "Distillate",
        "Concentration",
        "Essence",
        "Tincture",
        "Secretion",
        "Discharge"
],

"oils":[
        "Juice",
        "Sap",
        "Solution",
        "Oil",
```

```
        "Liquid",
        "Extract",
        "Distillate",
        "Concentration",
        "Essence",
        "Tincture",
        "Secretion",
        "Discharge"
    ],

    "gases":[
        "Gas",
        "Vapour",
        "Essence",
        "Air",
        "Extract",
        "Fumes",
        "Smoke",
        "Spray",
        "Steam",
        "Mist"
    ],
```

```
"amber":[
        "Amber",
        "Crystal",
        "Gem",
        "Quartz"
],

"gem":[
        "Crystal",
        "Gem",
        "Quartz"
],

"ore":[
        "Ore",
        "Minerals",
        "Rock",
        "Chunks",
        "Pieces"
],

"pellets":[
        "Pellets",
```

"Granules",

"Grains",

"Precipitate",

"Chunks",

"Pieces"

],

"rbflask":[

"Juice",

"Sap",

"Solution",

"Oil",

"Liquid",

"Extract",

"Distillate",

"Concentration",

"Essence",

"Tincture",

"Secretion",

"Discharge"

],

"shavings":[

```
            "Filings",
            "Shavings",
            "Residue"
    ],

    "pills":[
            "Pill"
    ],

    "creams":[
            "Cream"
    ],

    "sachets":[
            "Sachet"
    ],

    "syringes":[
            "Syringe"
    ],

    // CHEMICAL NAMES - These do not need to be translated
    "chemicalStarts":[
```

"Adamant",

"Bot",

"Cal",

"Cad",

"Dec",

"Et",

"Ab",

"Acer",

"Def",

"Ex",

"Fruc",

"Grat",

"Hod",

"Ir",

"Jud",

"Ap",

"Laet",

"Med",

"Onus",

"Ret",

"Pat",

"Pro",

"Quar",

```
            "Redon",
            "Satag",
            "Unus",
            "Velox",
            "Vult",
            "Quen",
            "Xen"
    ],
    // These do not need to be translated
    "chemicalEnds":[
            "ene",
            "ine",
            "ite",
            "aphos",
            "erene",
            "alene",
            "iphos",
            "amine",
            "amycin",
            "omycin",
            "achurin",
            "inon",
            "on",
```

"onsite",

"aside",

"oxide",

"ivied",

"ox",

"it ox",

"detox",

"it ox",

"alite",

"alike",

"ick",

"acute",

"tin",

"in",

"optic",

"attic",

"ate",

"ani",

"oxen",

"toxin",

"a toxin",

"Ulin",

"oleic",

```
            "Alic",
            "Ilic",
            "one",
            "ozone",
            "atone",
            "atone"
        ]
}
```

STRINGS-EN SOURCE CODE

```
[
    //ADDED IN MOD

    {"code":"loading","text":"Prompt 1..."},
    {"code":"CarbonicAnhydraseInhibitortitle","text": "Carbonic Anhydrase Inhibitor"},
    {"code":"retention","text":"Reduces Fluid Retention"},

    {"code":"brand_retention","text":"{0} Reduces Fluid Retention"},

    // Advisors
    {"code":"random","text":"Random"},
    {"code":"Leonard","text": "Leonard"},
```

{"code":"jenny","text":"Jenny"},

{"code":"Chan","text": "Chan"},

{"code":"sashay","text": Sasha"},

{"code":"Orion","text": Orion"},

{"code":"penny","text":"Penny"},

{"code":"Barclay","text": "Barclay"},

{"code":"Tess","text": Tess"},

{"code":"company.Leonard","text”: “REPRESENTATIVE COMPANY"},

{"code":"company.jenny","text":" REPRESENTATIVE COMPANY "},

{"code":"company.Chan","text":" REPRESENTATIVE COMPANY "},

{"code":"company.sashay","text":" REPRESENTATIVE COMPANY "},

{"code":"company.Orion","text":" REPRESENTATIVE COMPANY "},

{"code":"company.penny","text":" REPRESENTATIVE COMPANY "},

{"code":"company.Barclay","text":" REPRESENTATIVE COMPANY "},

{"code":"company.Tess","text":" REPRESENTATIVE COMPANY "},

// Side effects - no catalyst

{"code":"narrowed pupils","text": "Narrows Pupils"},

{"code":"sleepiness","text":"Prompts Sleepiness"},

{"code":"dry mouth","text": "Dries Mouth"},

{"code":"constipation","text":"Causes Constipation"},

{"code":"headaches","text":"Causes Headaches"},

{"code":"nanoneedles","text":"Causes pins and needles"},

{"code":"nausea","text":"Induces Nausea"},
{"code":"dizziness","text":"Causes Dizziness"},
{"code":"fatigue","text":"Causes Fatigue"},
{"code":"highbloodpressure","text": "Increases Blood Pressure"},
{"code":"inflames skin","text": "Inflames Skin"},
{"code":"nightmares","text":"Induces Nightmares"},
{"code":"brand_nausea","text":"{0} nauseated"}
]

APPENDIX 3. CHAPTER 6 SUPPLEMENT

S.M.A.R.T Prompts

Prompt 1: S.M.A.R.T

- *Specific* - Specific amount is specified in-game.
- *Measurable* - Money made
- *Assignable* - The player.
- *Realistic* - Players should have completed tutorials and one in-game challenge making the possibility for them to make profit in the game realistic.
- *Time-related* - One gameplay session.

You will be cast into the role of a small Acetazolamide L.T.D. manufacturing company.

Your goal is to make your company as profitable as possible. That is, make the most money possible within the game session. You will only be given this one chance. You will have to make decisions along the way and ensure you are keeping up with FDA regulations. Remember by following your standard operating procedures (SOP's) will ensure you stay on FDA's good side. After all, we would not want to end up with a 483!

Some things to keep in mind:

Although the game does not (directly) require or display a reserve osmosis water purification system such as the one in Figure 1 below. We must pretend it does since water is an essential component of Acetazolamide manufacturing (See Acetazolamide Manufacturing). Additionally, we will assume that syringe-type items in the game are

products of the lyophilization (freeze-dry) process necessary to manufacture injectable Acetazolamide. For additional information on relevant manufacturing equipment, click here. Since you are an injectable Acetazolamide manufacturer you will need to make injectable products (syringe products).

Prompt 2: S.M.A.R.T

- *Specific* - Gain 10 quality points (QPs)
- *Measurable* - Quantitative point system
- *Assignable* - The player.
- *Realistic* - Players should have completed tutorials and one in-game challenge making the possibility for them to play out all required actions possible.
- *Time-related* - One gameplay session.

You will be cast into the role of a small Acetazolamide L.T.D. manufacturing company.

Your goal is to gain 10 quality points (QPs). See the Quality Rubric to find out exactly how to gain each QP.

You will only be given this one chance. You will have to make decisions along the way and ensure you are keeping up with FDA regulations. Remember by following your standard operating procedures (SOP's) will ensure you stay on FDA's good side. After all, we would not want to end up with a 483!

Some things to keep in mind:

Although the game does not (directly) require or display a reserve osmosis water purification system. We must pretend it does since water is an essential component of Acetazolamide manufacturing (See Acetazolamide Manufacturing). Additionally, we will assume that syringe-type items in the game are products of the lyophilization (freeze-dry) process necessary to manufacture injectable Acetazolamide. For additional information on relevant manufacturing equipment, click here. Since you are an injectable Acetazolamide manufacturer you will need to make injectable products (syringe products).

Prompt 3: S.M.A.R.T

- *Specific* - Gain quality points (QPs) and profit. This one's a bit more vague than the other prompts.
- *Measurable* - Quantitative point system, Currency
- *Assignable* - The player.
- *Realistic* - Players should have completed tutorials and one in-game challenge making the possibility for them to play out all required actions possible.
- *Time-related* - One gameplay session.

You will be cast into the role of a small Acetazolamide L.T.D. manufacturing company.

Your goal is to gain the most profit and quality points (QPs) possible. See the Quality Rubric to find out exactly how to gain each QP.

You will only be given this one chance. You will have to make decisions along the way and ensure you are keeping up with FDA regulations. Remember by following your

standard operating procedures (SOP's) will ensure you stay on FDA's good side. After all, we wouldn't want to end up with a 483!

Some things to keep in mind:

Although the game does not (directly) require or display a reserve osmosis water purification system. We must pretend it does since water is an essential component of Acetazolamide manufacturing (See Acetazolamide Manufacturing). Additionally, we will assume that syringe-type items in the game are products of the lyophilization (freeze-dry) process necessary to manufacture injectable Acetazolamide. For additional information on relevant manufacturing equipment, click here. Since you are an injectable Acetazolamide manufacturer you will need to make injectable products (syringe products).

The FDA has approved you to manufacture Acetazolamide only.

SHELL SCALE

Seven GxP tasks were presented. High scores are good. The player's shell score corresponds to the total number of tasks performed correctly. If applicable unprompted task (null) are assumed to be ethically performed.

0-Player took every available shortcut

1-One ethical task performed.

2-Two ethical tasks performed

3-Three ethical tasks performed

4-Four ethical tasks performed

5-Five ethical tasks performed.

6-Six ethical tasks performed.

7-Player was completely ethical and performed all tasks correctly.

CATEGORICAL DESCRIBERS

Sold subpotent drugs- When players are flagged for selling subpotent drugs it means that the player did not process the ingredients to the highest API therapeutic game concentration. The only exception in the game is when the player lowers the ingredient concentration to minimize side effects (hence providing a better quality drug).

Concealing clinical results - When players are flagged for concealing clinical results it means the player ran a clinical trial and chose not to publicly disclose all the results. (Typically revealing negative results harms game sales. Players who hide negative results still risk being caught and further damaging their game sales.)

Sold unapproved drugs using cheaper materials - When players are flagged for selling unapproved drugs using cheaper materials it means the player chose to process the drug to be orally administered (game capsules). This was unethical because the players were instructed to only sell injectable drugs (game syringes). In addition, players were given approval to produce one and only one injectable drug.

Sold unapproved drugs- When players are flagged for selling unapproved drugs it means the player chose to sell two or more drugs. This was unethical because the players were given approval to produce one and only one injectable drug. The only exception to this was if the player upgraded their drug to make it of better quality and continued to sell the "standard" version of the drug in addition to the "upgraded" drug (e.g. marketing a standard release and extended release version).

Price hike- When players are flagged for price hiking it means the players chose to markup the price of their drug 27.5% or greater. Where 27.5% is the median % markup used by players at the end of their prompt 1,1.2,and 1.3 games.

ETHICAL SCALE

0 - Completely unethical. Did not follow guidelines at all.

1-Very unethical. Followed guidelines when convenient. Only acting ethically when something was to be gained. For example, running a clinical trial to boost sales. Or only maximizing drug potency when the maximum concentration was the easiest product to process.

2- Somewhat unethical. Followed guidelines to a minimum. Some ethical actions but mostly unethical behavior.

3-Somewhat ethical. Followed guidelines with some unethical actions. Or if acting unethically typically corrects actions.

4-Very ethical. Followed guidelines moderately. Typically breaking guidelines under acceptable exceptions.

5-Ethical. Followed all guidelines perfectly.

BIGPHARM'S QUALITY RUBRIC

Quality points (QP) will be gained as you progress through the game. The amount of quality points you gain will depend on your actions.

There are 10 possible QP's. Here is how they are gained.

Cleaning Your Facility - 1 QP

As you have played through BigPharma you may have noticed dirt on the walls. Clean the dirt off the walls by painting your tiles to gain this QP. Or don't the choice is yours! Click here for a step-by-step example.

Maximizing Drug Concentrations - 2 QP

As you have played through BigPharma you may have noticed drugs have a range of active concentrations. Max this value out to gain 2 QP. Or don't the choice is yours! Click here for a step-by-step example.

Analyze your Drugs - 1 QP

Use the analyzer on all drugs produced to gain this QP. Click here for a step-by-step example.

Analyze your Ingredients - 1 QP

Use the analyzer on all drugs produced to gain this QP. Click here for a step-by-step example.

Clinically testing your Drugs - 2 QP

Run a clinical trial for each drug you produce. Click here for a step-by-step example.

Implementing Tracing - 1 QP

The FDA requires a paper trail for all drugs sold in the US. To make sure you have proper identification of your products use a packer. Click here for a step-by-step example.

Taking Inventory - 1 QP

For quality to be ensured all your products should be accounted for. Use a stock gate on your product lines to conduct inventory. Click here for a step-by-step example.

Continuous Improvement- 1 QP

Upgrade at least one drug to get this QP. Click here for a step-by-step example.

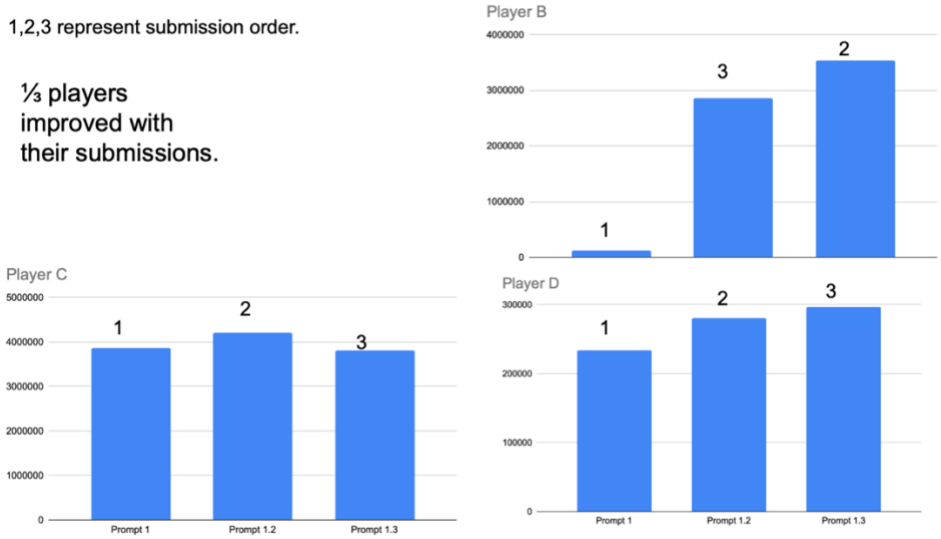

Figure S3.1: Summarizes Player vs earning in-game revenue by game. Where numbers above bars are the players' respective submissions.

From Figure S3.1 we see that only 1 in 3 players improved with their submission. Player B appears to improve with time until a closer look at the submission order reveals that Player B in fact performed poorer in their last submission compared to their second. Player C improved moving from Prompt 1 to 2 but then slightly decreased in Prompt 3- their last submission. Lastly, Player D who improved over time only did so gradually in terms of in-game revenue.

It should be noted that Player B's counterintuitive submission order was due to a technical difficulty. Indeed, Player B attempted to play the Prompt 2 after Prompt 1 but the screen recording device crashed. As a result Player B (who played entirely remote) proceeded to Prompt 3 before returning to the Prompt 2 game.

SUMMARY TABLES

The following legend is to be used in Tables S3.1, S3.2, and S33.

Where red cells represent the presence of game or management fraud and green cells resent the absence of worker or management fraud.

X	Present
0	Absent

Table S3.1: Summarizes players' absence or presence of worker and management fraud.

	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

Table S3.2: Summarizes players' absence or presence of worker and management fraud. With worker tasks collapsed.

	Player A	Player B	Player C	Player D	
Task 1	0	0	0	0	
Task 2	0	0	X	0	
Task 3	0	0	X	0	
Task 4	0	0	X	0	
Task 2.1	null	null	X	null	
Task 2.2	null	null	0	null	
Management Fraud	o	X	X	X	Prompt 1
Task 1	0	0	0	0	
Task 2	0	0	0	0	
Task 3	0	0	0	0	
Task 4	0	0	0	0	
Task 2.1	null	null	null	null	
Task 2.2	null	null	null	null	
Management Fraud	X	X	X	X	Prompt 2
Task 1	0	0	0	0	
Task 2	0	0	0	0	
Task 3	0	0	0	0	
Task 4	0	0	X	0	
Task 2.1	null	null	null	null	
Task 2.2	null	null	null	null	
Management Fraud	X	X	X	X	Prompt 3

Table S3.3: Summarizes players' absence or presence of worker and management fraud. With management frauds collapsed.

	Player A	Player B	Player C	Player D	
Sold unapproved drug	0	X	X	X	
Sold subpotent drugs	0	X	X	X	
Used cheaper/unapproved material	0	X	X	X	
Conceal negative clinical results	0	0	0	0	
Price Hike	0	-	X	X	
Worker Fraud	0	0	X	0	Prompt 1
Sold unapproved drug	X	0	X	0	
Sold subpotent drugs	0	X	X	E	
Used cheaper/unapproved material	0	X	X	0	
Conceal negative clinical results	0	0	0	0	
Price Hike	0	X	X	X	
Worker Fraud	0	0	0	0	Prompt 2
Sold unapproved drug	0	0	X	0	
Sold subpotent drugs	X	X	E	E	
Used cheaper/unapproved material	0	0	X	0	
Conceal negative clinical results	0	0	0	0	
Price Hike	X	X	X	X	
Worker Fraud	0	0	X	0	Prompt 3

Table S3.4 and S3.5: Shell scores per player are summarized. Additionally, the overall averages and median shell scores are presented along with overall player averages and median shell scores.

	Player A	Player B	Player C	Player D	Average	Median
Prompt 1	7	7	2	7	5.75	7
Prompt 2	7	7	7	7	7	7
Prompt 3	7	7	6	7	6.75	7
Average	7	7	5	7		
Median	7	7	6	7		

Overall Shell Score- Average	6.5
Overall Shell Score- Median	7

Table S3.6 and S3.7: Ethical scores per player are summarized. Additionally, the overall averages and median ethical scores are presented along with overall player averages and median ethical scores.

	ES-Prompt 1	ES-Prompt 2	ES-Prompt 3	Average	Median
Player A	5	3	3	3.67	3
Player B	0	3	3	2	3
Player C	1	1	1	1	1
Player D	4	4	4	4	4
Player's ES Average per Prompt	2.5	2.75	2.75		
Player ES Median per Prompt	2.5	3	3		

Overall ES Average	2.58
Overall ES Median	3

ETHICAL TIMETABLES

Purpose

Player's strategies are closely observed, and key events are documented in a ethics timeline table. After closely observing each players strategies in each primary prompt the players overarching strategy is described and the player is given an ethics score.

PLAYER A

PROMPT 1

Table S3.8: Player A's ethical time for Prompt 1.

Time(minutes)	Type	Notes
0-9:30	Ethical	Has multiple lines selling injectable at max concentration.
9:32	Ethical-E	Begins selling a upgraded version of the injectable at max concentration.
18:13		Deletes several lines
19:12		Is discounting the drug 20%. Losing money on standard drug.
19:14		Has taken out all three loans.
20:32		Deletes several lines.
39:53		Has repaid loans. Takes out another loan.

Summary: Player attempted to play very ethically though gets themselves into a massive amount of debt by taking out multiple loans. No shell fraud. Ethics score- 5.

PROMPT 2

Table S3.9 Player A's ethical time for Prompt 2.

Time(minutes)	Type	Notes
0-5:18	Ethical	Analyzing ingredient. Begins selling injectable at max concentration.
5:19	Ethical	Analyzing intermediates.
6:02	Unethical	Implements tracing onto one line and not the other.
6:50	Unethical	Begins selling subpotent version of same injectable. One process line with potency and one line with subpotent.
13:21	Ethical	Analyzing drug product.
15:23		Has taken out two loans.

Summary: Player attempted to play very ethically though gets themselves into a massive amount of debt by taking out multiple loans. Sells subpotent drugs. But does implement tracing. No shell fraud. Ethics score- 3.

PROMPT 3

Table S3.10 Player A's ethical time for Prompt 3.

Time(minutes)	Type	Notes
0-4:00	Ethical /Unethical	Selling injectable drug and analyzing everything. Potency. No tracing.
5:30	Unethical	Stops selling first injectable drug and begins selling subpotent form. No tracing.
7:32	Ethical	Begins implementing tracing.
8:08	Ethical / Unethical	Has tracing on one line and not the other.
8:40		Moves another line to tracing. Still has one more without.
9:51	Ethical	Has all lines traced now.
16:49	Ethical /Unethical	Has another line selling subpotent injectable. Line has trace.

Summary: Player attempted to play very ethically though gets themselves into a massive amount of debt by taking out multiple loans. Sells subpotent drugs. But does implement tracing. No shell fraud. Ethics score- 3.

Overall: Player was a bit of a mixed bag. Typically starts the games by selling an injectable drug at potency. Then early on stop selling the injectable at potency. Selling the injectable subpotent for the majority of the game. However, did typically implement tracing in lines. Player consistently lost money because of so many loans taken out. It should be noted that the player attempted to play ethically but was not seeing successful revenue (due to loans) at which point the strategy seems to change and the player begins selling subpotent products.

Overall ethics score- 3

PLAYER B

PROMPT 1

Table S3.11 Player B's ethical time for Prompt 1.

Time(minutes)	Type	Notes
No video		

Summary: Player did not submit a video. From photos the players made multiple lines selling creamers, and capsules. Subpotent. Though conducted no shell fraud. Prompt 1 in-game ethics score-0.

PROMPT 2

Table S3.12 Player B's ethical time for Prompt 2.

Time(minutes)	Type	Notes
2:37	Ethical	Cleans plant
7:05	Ethical	Cleans newly purchased section of plant
11:06	Ethical	Cleans newly purchased section of plant
11:33	Ethical/Unethical	Begins selling upgraded injectable. Subpotent. Process line has tracing
13:17		Takes out loan
19:47	Unethical	Begins selling another line of the same product. However, this time ran out of space for boxing machine and just implemented inventory device. It should be mentioned the player attempted to fit the boxer in several times just failed to ever put the puzzle together and gave up.
29:29	Ethical	Begins selling same upgraded injectable with another line this time implementing tracing.
29:34	Ethical	Cleans newly purchased section of plant
37:19		Hires scientist
63:25	Ethical	Begins selling same upgraded injectable with another line this time implementing tracing.

PROMPT 3

Table S3.13 Player B's ethical time for Prompt 3.

Time(minutes)	Type	Notes
7:00		Hires scientist
8:46	Ethical /unethical	Begins selling upgraded injectable. Subpotent. Process line has tracing.
9:03		Takes out loan
23:29	Unethical	Deletes analyzer
36:30	Ethical	Cleans plant
51:02	Ethical	Has several lines selling the sample injectable drug. Subpotent. With tracing.
56:45		Analyzer is being used on ingredients again.
66:03	Ethical	Has option to boosts sells by giving gifts to doctors but does not take it.
67:53	Ethical	Using analyzer on intermediates.

Overall: Player typically upgrades injectable drug and begins selling subpotent product. The facility is cleaned as they go typically before selling the product and the process lines typically have tracing before the selling of the product. Indeed, only one line within all

their play lacked tracing and this was due to a space issue. Most guidelines are followed to a tee minus the potency of the drug. The player develops multiple lines to see the same drug. Overall ethics score of 3.

PLAYER C

PROMPT 1

Table S3.14 Player C's ethical time for Prompt 1.

Time(minutes)	Type	Notes
0-1:49	Ethical	Analyzed ingredient to find side effects.
1:50	Unethical	Sells capsules subpotent.
4:32	Unethical	Sells another capsule drug. Also, subpotent.
6:02	Ethical	Hires scientist to research new ingredients.
7:50	Ethical	Analyzes new ingredient
10:10	Ethical / Unethical	Developed a new line with the new higher quality ingredient. Sells it at max concentration. But sells it as a capsule instead of an injectable.
17:51	Unethical	Begins developing another new line. The drug is ungraded and made with a higher quality ingredient. Sells subpotent. Sells as capsule.
20		Hired more scientist.

22	Ethical	Analyzes new ingredients
24:09		Begins developing another new line.
30:07		Continuing to build line. Paused build to analyze the ingredient.
30:22	Ethical	Hired more scientist
30:47		Takes out loan
33:51	Ethical / Unethical	New line is finished. Begins selling a highly upgraded injectable. Subpotent.
35:17	Ethical	Pays back loan
49:47		Begins selling another highly upgraded injectable drug. Subpotent.
55:29		Merges the two highly upgraded ingredients into one ingredient.
62:03	Ethical / unethical	Begins selling the combined highly upgraded drug as a combined drug. Injectable. No side effects. Sold subpotent for both active ingredients.
68:01		Begins new line.
84:05		Takes out another loan
89:58	Ethical	Begins selling a vaccine with no side effects. That also acts as a combination drug.

Figure S3.2: Highest level of combination therapy achievable in-game. Player C begins selling this at time stamp 89:58.

Overall: Player starts off by selling unapproved capsules. Before developing an upgraded injectable. The player typically only maximizes drug concentration when convenient. Sells subpotent products. But the player continues to upgrade the product. Eventually turning the product into highly specialized combinations drugs that can be sold a very high sticker price compared to the standard drugs.

Overall ethics score- 1.

PROMPT 2

Table S3.15 Player C's ethical time for Prompt 2.

Time(minutes)	Type	Notes
1:06	Unethical	Sells capsule. Full potency. No side effects.

2:02		Begins new line.
16:21	Ethical / unethical	Begins selling a highly upgraded injectable. No side effects. Subpotent.

Figure S3.3: Example of highly upgraded in-game drug.

21:24	Ethical	Begins implementing tracing.
33:06	Ethical / unethical	Begins selling highly upgraded combination therapy. Injectable. Subpotent.
39:07	Ethical	“Cleans” plant
41:27	Ethical	Hired scientists
49:47	Ethical	Cleaned newly purchased section of plant
55:28	Ethical / unethical	Begins selling another combination drug. Injectable. Max concentration.

57:48	Ethical	Stops selling unapproved capsule drugs.
77:06	Ethical	Cleaned newly bought section of plant.
83:48	Ethical	Implements tracing fully
84:01	Ethical	Begins selling vaccine. Full concentration.

PROMPT 3

Table S3.16 Player C's ethical time for Prompt 3.

Time(minutes)	Type	Notes
8:02		Second loan taken out
8:10	Ethical / unethical	Begins selling highly upgraded injectable. Subpotent.
13:06	Unethical	Begins selling another drug. Capsule. Subpotent.
31:19	Ethical	Begins selling a combination therapy. Upgrade from injectable. Stopped selling other injectable. Subpotent.
32:53	Ethical	Stopped selling capsules.
33:03	Ethical	Cleans plant

37:01	Ethical	Implements tracing
47:47	Ethical	Cleans newly bought sections of plant.
68:18	Ethical	Begins selling an upgraded version of the combination drug. This time with three cures. No side effects. Full potency.
68:37	Ethical	Implements tracing
69:04		Hires scientists

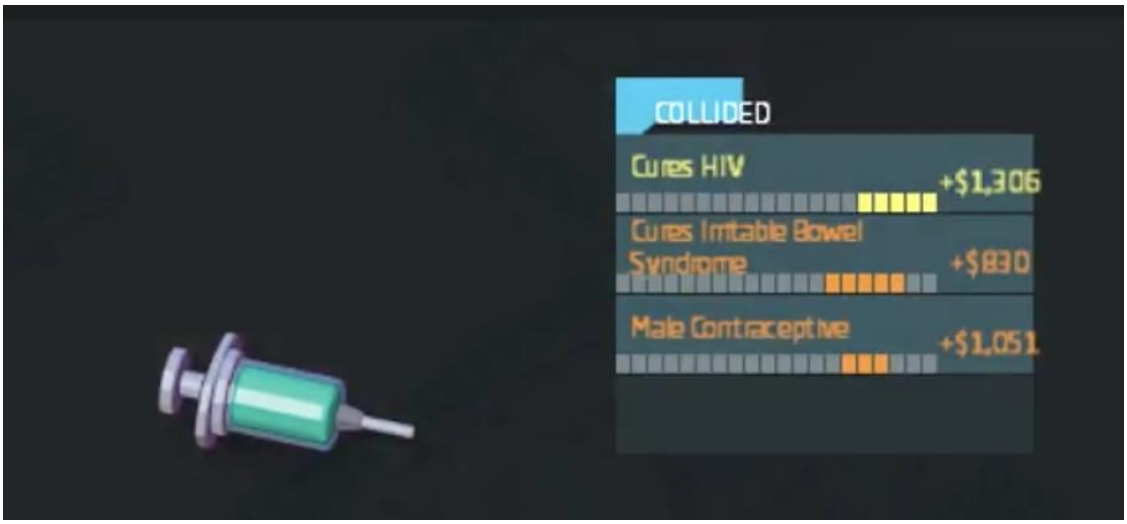

Figure S3.4: Highest level of combination therapy achievable in-game. Player C begins selling this at time stamp 68:18.

Overall: Typically began injectable development by upgrading ingredients. Analyzed ingredients and researched into buying new ingredients throughout the game. Would typically produce two upgraded injectable products one or more was typically sold subpotent. The player then merged the two active ingredients into one to produce a combination therapy. Then continue to upgrade this therapy until it cured three illnesses.

Products typically did not contain side effects. While the injectable drug was in development typically sold unapproved capsules “on the side”. Prompt 1.2 and 1.3 the player stopped selling the capsules once the injectable was fully developed. Prompt 1 the player sold the capsules the entire game. The player typically did implement tracing into process lines until the end of the game. And typically, only implemented tracing into one line.

Overall, ethics score - 1.

PLAYER D

PROMPT 1

Table S3.17 Player D’s ethical time for Prompt 1.

Time(minutes)	Type	Notes
4:57	Unethical	Begins selling subpotent injectable.
9:23		Has deleted line.
10:53	Ethical-E	Begins selling a drug. Subpotent. But to minimize side effects.

Summary: Player starts out by selling a subpotent injectable. But quickly upgrades the drug. Sells subpotent but under the exception that the player was attempting to minimize drug side effects.

Prompt 1, ethics score - 4.

PROMPT 2

Table S3.18 Player D's ethical time for Prompt 2.

Time(minutes)	Type	Notes
0-5:39	Ethical	Completely ethical even upgraded drug and sold it at max concentration.
5:40	Unethical	Deletes analyzer
6:10	Unethical	Only Cleans dirty spots
7:41	Ethical	Changes line to minimize side effects.
14:05	Ethical	Starts to implement tracing (boxer and inventory)

PROMPT 3

Table S3.19 Player D's ethical time for Prompt 3.

Time(minutes)	Type	Notes
0-4:38	Ethical	
4:39	Unethical	Deletes analyzer
5:40	Ethical	Implements tracing

Overall: Develop the same drug throughout the prompts. Typically selling the drug at max concentration until the analyzer reveals concentration at which side effects are worse. Then the player adjusted the drug concentration to minimize the side effects of the ingredients. Prompt 1 the player sold unapproved capsules. This did not occur in Prompt 2 and 3. Overall, ethics score - 4.

CREAVITIY AND IMAGINATION OF PLAYERS A PROCESS LINE EXAMPLE

Player D in Prompt 1 provides an excellent example of the games ability to capture imagination and creativity. Below is Player D's Prompt 1 process line. As can be seen from Figure S3.5 the player added two additional syringe machines to their process compared to the one in the investigator's theorized process (see Figure 6.5).. This allowed for the player to produce 3x the product in the same amount of time.

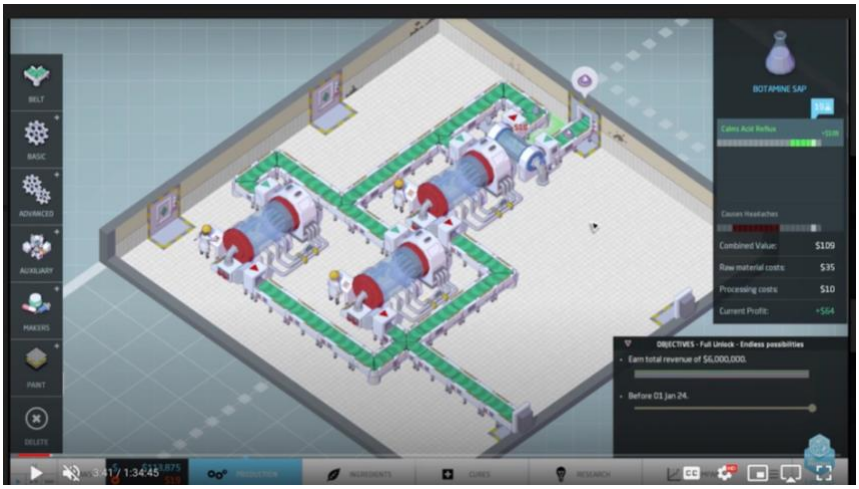

Figure S3.5: Screenshot of Player D's prompt 1 processing plant.

Additionally, we see that Player D analyzed drugs something not required in Prompt 1 (See Figure 3.6). Regardless this scene captures one of countless ways players could potentially cheat in-game. As the player analyzed separately imported ingredients. An action analogous to if a drug manufacturer only tested and reported superior product and not the poor-quality materials.

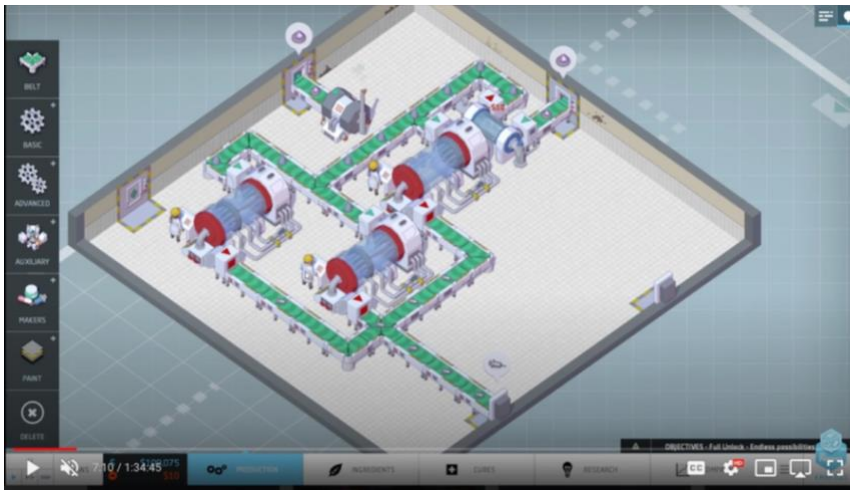

Figure S3.6: Screenshot of Player D's prompt 1 processing plant with analyzer.

APPENDIX 4. CHAPTER 7 SUPPLEMENT

TOURNAMENT PROPOSAL

To host the BigPharma tournament at the esports UK gaming lounge a proposal had to be submitted. The details are provided below.

Figure S4.1 Imagine presented in BigPharma Tournament Proposal

Proposed by: Robert A. Lodder (lodder@g.uky.edu) and Heather R. Campbell (hrca227@g.uky.edu)

Proposed Location: UK Cornerstone E-Sports Lounge

Prizes: 1st: $100 2nd: $50 3rd: $30.

Entry Requirement: Own BigPharma on Steam (cost $ 27.88)

This is a three-day event.

Dates: April 9-11, 2021

Friday April 9th- Night Practice. Players will be taught how to use Jupyter notebooks in combination with BigPharma. Players will also learn how to load mods into BigPharma. Time will be allotted in the practice period for players to familiarize themselves with the game itself.

Saturday April 10th- Practice and Competition. Additional practice time will be given to players for those unable to make the Friday night practice.

Sunday April 11th- Competition Day

Players will be asked to play through three specific scenarios in BigPharma. Player who makes the most money wins! (Sum of the three scenarios). Players can play the three scenarios as many times as they wish during the tournament.

ETHICAL SCORE CALCULATIONS

The overall ethical score was calculated as the average or median of the players' ES' within prompts and are labeled appropriately throughout.

Table S4.1 and S4.2 The average and median ethical scores earned by players in Prompt 1, 2, and 3.

Overall ES Average	2.33
Overall ES Median	2

	ES-Prompt 1	ES-Prompt 2	ES-Prompt 3	Player Overall ES- Average	Player Overall ES- Median
Player T1	2	2	2	2.00	2
Player T2	0	4	4	2.666666667	4
Player's ES Average per Prompt	1	3	3		
Player ES Median per Prompt	1	3	3		

PRE-TOURNAMENT VS. TOURNAMENT OVERALL ETHICAL SCORES

Table S4.3 and S4.4 Comparison of ethical scores in non-tournament (labeled pre-tournament to signify order) and tournament environments.

Pre-tournament		Tournament	
Overall Average	Overall Median	Overall Average	Overall Median
2.58	3	2.33	2

	Pre-tournament		Tournament	
	Player's ES Average per Prompt	Player ES Median per Prompt	Player's ES Average per Prompt	Player ES Median per Prompt
Prompt 1	2.5	2.5	1	1
Prompt 2	2.75	3	3	3
Prompt 3	2.75	3	3	3

PRICE HIKE PERCENTAGE DETERMINATIONS

Price hikes were defined based on the median % markup used by players in players' in prompt 1,2, and 3. Below presents the non-tournament player markups and tournament players % markups.

Non-tournament players
27.5% is the median % markup used by players at the end of their prompt 1,2, and 3 games.

Table S4.5 Summarizes the endgame % markup of drugs in pre-tournament setting by player. Where yellow cells were determined to be price hikes.

	Player A	Player B	Player C	Player D
Prompt 1	15		30	53
			10	-10
			-10	5
			40	12
Prompt 1.2		25	35	39
			20	
			20	
Prompt 1.3	30	30	50	39

Tournament Players
10% is the median % markup used by players at the end of their prompt 1,1.2,and 1.3 games.

Table S4.6 Summarizes the end-game % markup of drugs in tournament setting by player. Where yellow cells were determined to be price hikes.

Player T1 % Markups prompt 1		Player T2 % Markups prompt 1	
18	10	-20	
7	10		
10	10		
-20			
Player T1 % Markups prompt 1.2		Player T2 % Markups prompt 1.2	
10	5	38	
10	5		
8	5		
10			
Player T1 % Markups prompt 1.3		Player T2 % Markups prompt 1.3	
10		36	
10			
5			

Tables S4.7 and S4.8 summarizes the differences in price hike occurrences using the above definitions of price hike. That is one with a median of 27.5% and the other with a median of 10%.

Table S4.7 and S4.8 Summarizes the occurrences of management frauds with the different definitions of price hiking.

	Prompt 1	Prompt 1.2	Prompt 1.3
Sold unapproved drug	1	0	0
Sold subpotent drugs	1	2	2
Used cheaper/unapproved material	2	1	1
Conceal negative clinical results	1	0	0
Price Hike by tournament median	1	1	1
	6	4	4

10% median tournament

Either way we do see the occurrences of management fraud decrease once quality is introduced.

	Prompt 1	Prompt 1.2	Prompt 1.3
Sold unapproved drug	1	0	0
Sold subpotent drugs	1	2	2
Used cheaper/unapproved material	2	1	1
Conceal negative clinical results	1	0	0
Price Hike by primary median	0	1	1
	5	4	4

27.5% median no tournament

The effect of the Price Hike definition on pre-tournament versus tournament management fraud frequencies are present in Table S4.9.

Table S4.9 Summaries the frequencies of management fraud in non-tournament vs tournament environments using the two definitions of price hiking.

Technique	% Total Occurence in Tournament	% Total Occurence in Primary Study
Sold unapproved injectable drug	16.67%	50.00%
Sold subpotent drugs	83.33%	58.33%
Used cheaper/unapproved material	66.67%	41.67%
Conceal negative clinical results	16.67%	0.00%
Price Hike 27.5% median no tournament	33.33%	83.33%
	50.00%	10% median tournament

FREQUENCY CALCULATIONS

Summarizes the calculations of the above frequencies.

Table S4.10 Summary of management frauds taken place in games Prompt 1,2, and 3 in tournament environment.

	Tournament					
	Prompt 1	Prompt 2	Prompt 3	Total	Frequency	out of 6 games
Sold unapproved drug	1	0	0	1	17%	
Sold subpotent drugs	1	2	2	5	83%	
Used cheap/unapproved material	2	1	1	4	67%	
Conceal negative clinical results	1	0	0	1	17%	
Price Hike	1	1	1	3	50%	
Total	6	4	4	14		

Table S4.11 Summary of management frauds taken place in games Prompt 1,2, and 3 in non-tournament environment.

	Pre-Tournament					
	Prompt 1	Prompt 2	Prompt 3	Total		
Sold unapproved drug	3	2	1	6	50%	out of 12 games
Sold subpotent drugs	3	2	2	7	58%	
Used cheap/unapproved material	3	1	1	5	42%	
Conceal negative clinical results	0	0	0	0	0%	
Price Hike	3	3	4	10	83%	

Total	12	8	8	28		

APPENDIX 5. CHAPTER 8 SUPPLEMENT

ETHICAL TIMETABLES

Purpose

Player's strategies are closely observed, and key events are documented in a ethics timeline table. After closely observing each players strategies in each primary prompt the players overarching strategy is described and the player is given an ethics score.

PLAYER A

Table S5.1 Player A's ethical time for Prompt 1.0.2.

Time(minutes)	Type	Notes
3:02	Ethical	Has a injectable line running at max concentration.
5:56	Ethical	Has a second line for the same injectable running.

Summary: Player played completely ethically. Just setup lines inefficiently and lost money due to this. ES-5

PLAYER B

Table S5.2 Player B's ethical time for Prompt 1.0.2.

Time(minutes)	Type	Notes
5:08	Unethical	Begins selling an injectable with no API.
10:27	Ethical	Begins selling injectable with API. At max concentration.
33:48	Ethical / Unethical	Begins selling an upgraded version of the drug. Subpotent.
88:07	Unethical	Starts selling an inactive aka no API injectable again.

Summary: Player starts out by selling a completely inactive injectable. Eventually upgraded this to a subpotent upgraded ingredient version. This is what is sold much of the game. But right at the end the player creates a new line and starts selling inactive injectables again. Did typically have some form of tracing on lines.

PLAYER C

Summary-Unethical

PLAYER D

Summary-Ethical

APPENDIX 6. CHAPTER 9 SUPPLEMENT

AMENDED QUALITY RUBRIC

Below presents the amended quality rubric as presented to players in the Prompt 1.2.1 game.

BigPharma's Quality Rubric

Quality points (QP) will be gained as you progress through the game. The amount of quality points you gain will depend on your actions.

There are 10 possible QP's. Here is how they are gained.

Cleaning Your Facility - 1 QP

As you've played through BigPharma you may have noticed dirt on the walls. Clean the dirt off the walls by painting your tiles to gain this QP. Or don't the choice is yours! Click here for a step-by-step example.

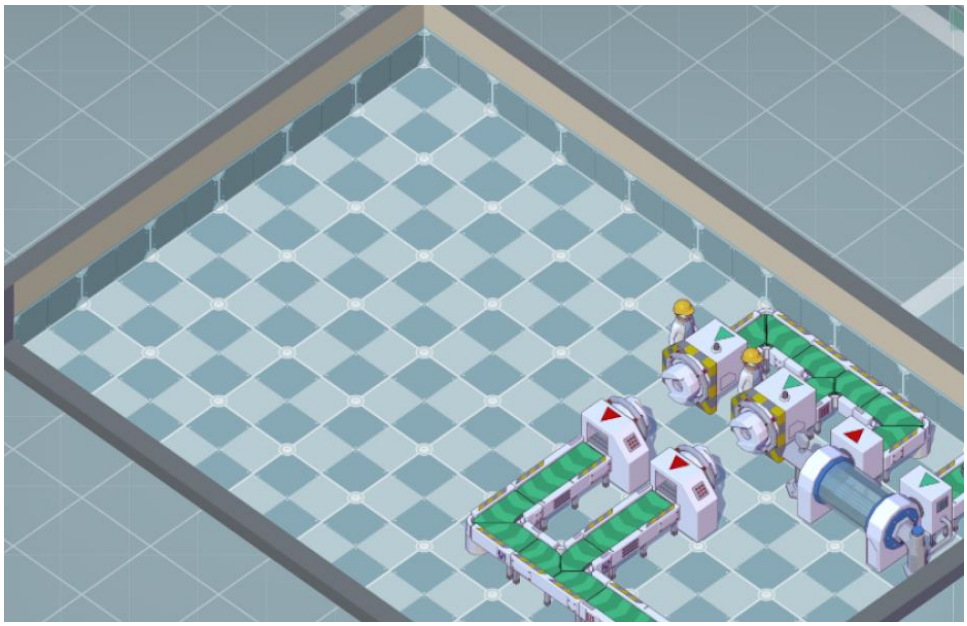

Figure S6.1 Depicts a clean facility.

Maximizing Drug Concentrations - 2 QP

As you've played through BigPharma you may have noticed drugs have a range of active concentrations. Max this value out to gain 2 QP. Or don't the choice is yours! Click here for a step-by-step example.

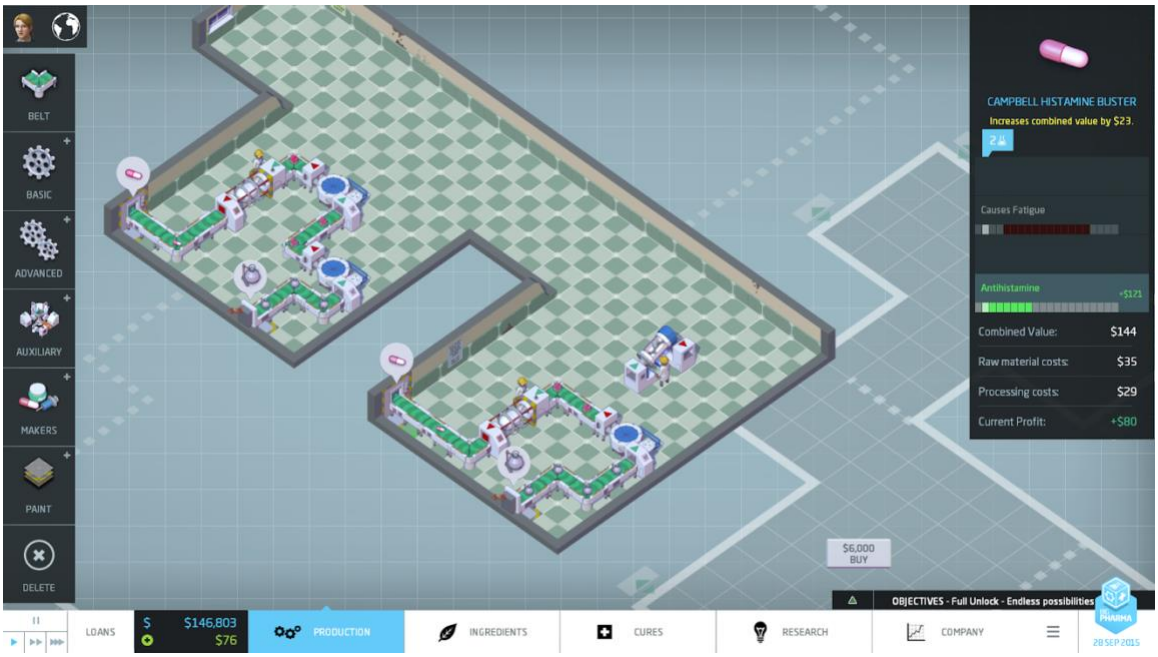

Figure S6.2 Depicts two process lines producing the same in-game drug capsule. The left line is manufacturing the drug at potency where the right line is selling subpotent drug. In-game concentrations are read through the green bar (top right). Where the white mark signifies the API concentration. Here the API is at its lowest concentration allowed while still gaining the in-game value for its therapeutic effects.

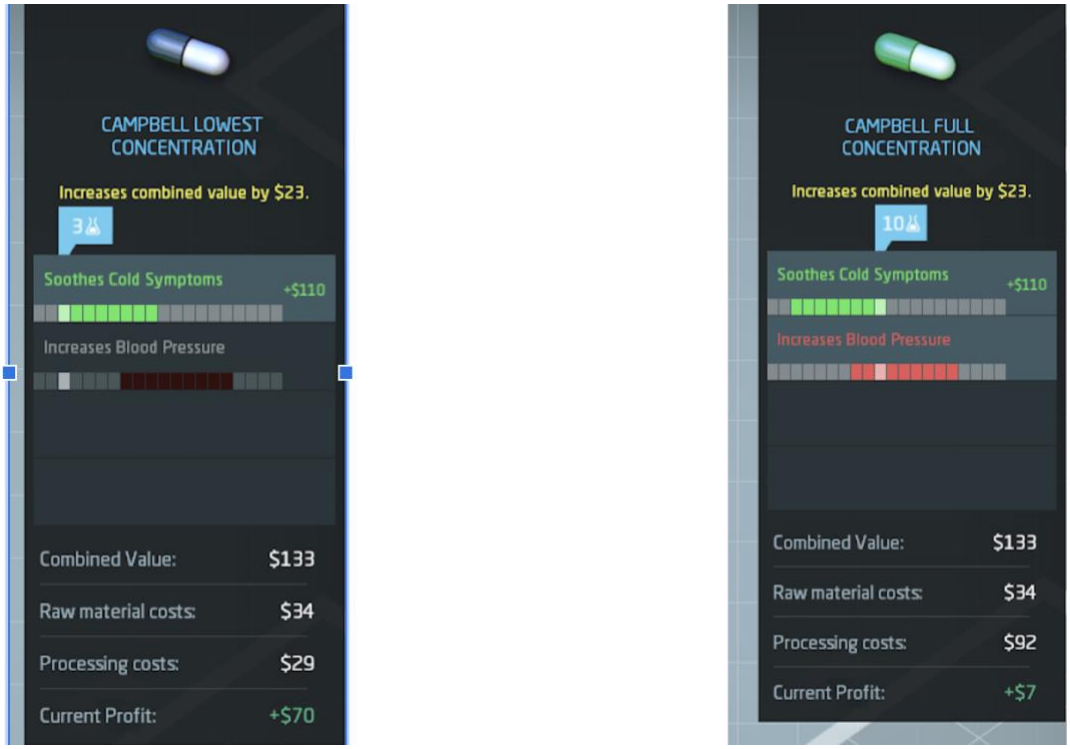

Figure S6.3 Depicts two identical in-game drugs. The left subpotent and the right potent. Note the white marker on the green bar signifies concentration level. With the blue beaker and value above the marker giving the numerical value of the API concentration. Note that selling sub potently results in a $70 profit per capsule where the potent drug only results in a $7 profit per capsule.

Analyze your Drug Product - 1 QP

Use the analyzer on your drug product (processed-syringe) throughout the game to gain this QP. This should be done before selling your drug, while selling your drug, and continue after the analyzer produces a result. Consider the analyzer a process analytical technology that the FDA requires you to use all the time. Click here for an example.

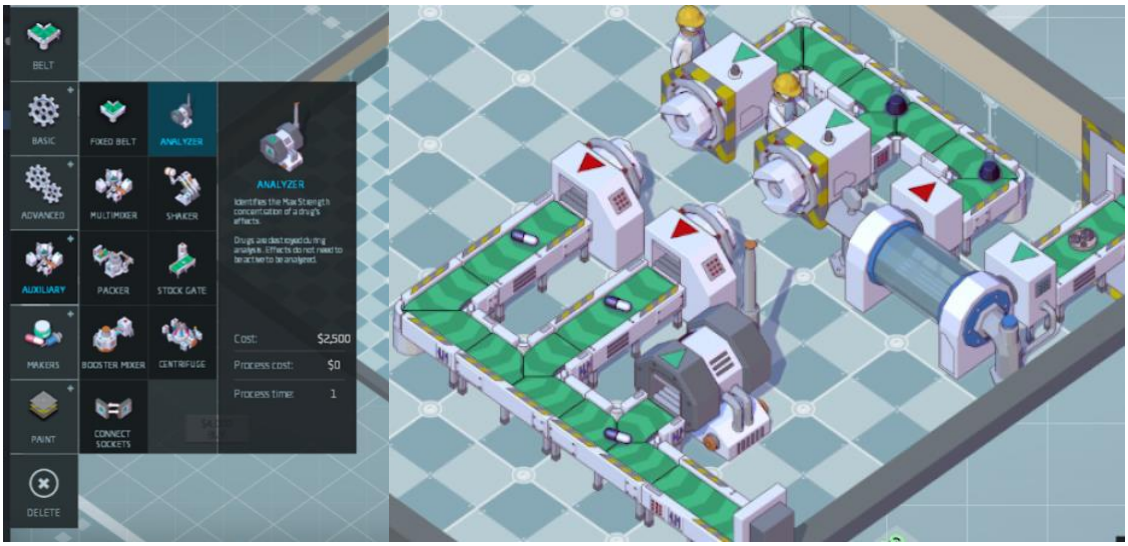

Figure S6.4 Example of analyzing ingredients Analyzer present on the left. Analyzer within the process line presented on the right

Analyze your Ingredients - 1 QP

Use the analyzer on all drug ingredients throughout the game to gain this QP. This should be done before selling your drug, while selling your drug, and continue after the analyzer produces a result. Consider the analyzer a process analytical technology that the FDA requires you to use all the time. Click here for an example.

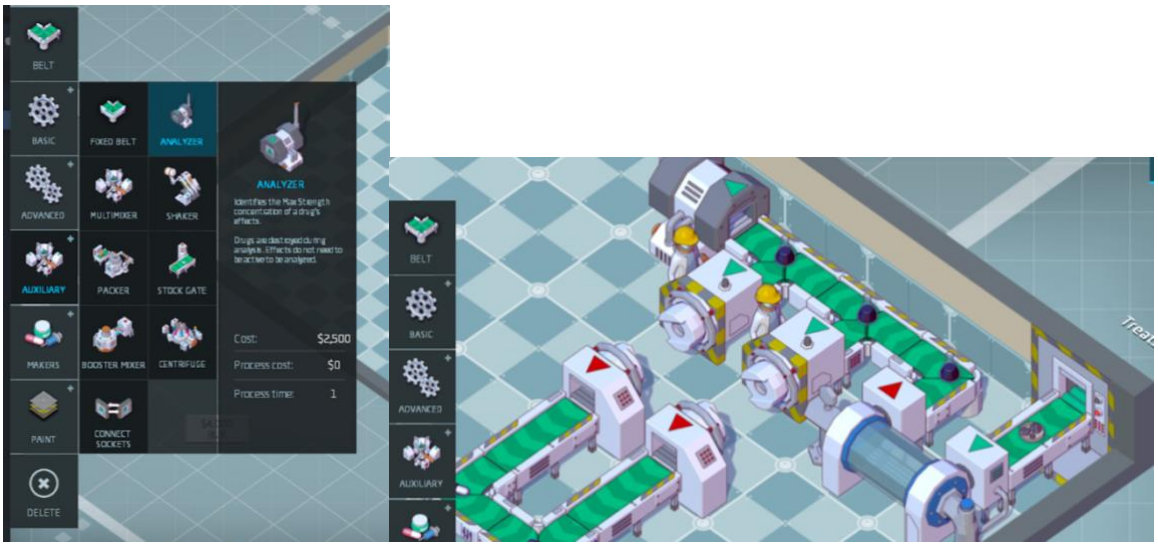

Figure S6.5 Example of analyzing ingredients Analyzer present on the left. Analyzer within the process line presented on the right.

Clinically testing your Drugs - 2 QP

Run a clinical trial for each drug you produce. Click here for a step-by-step example.

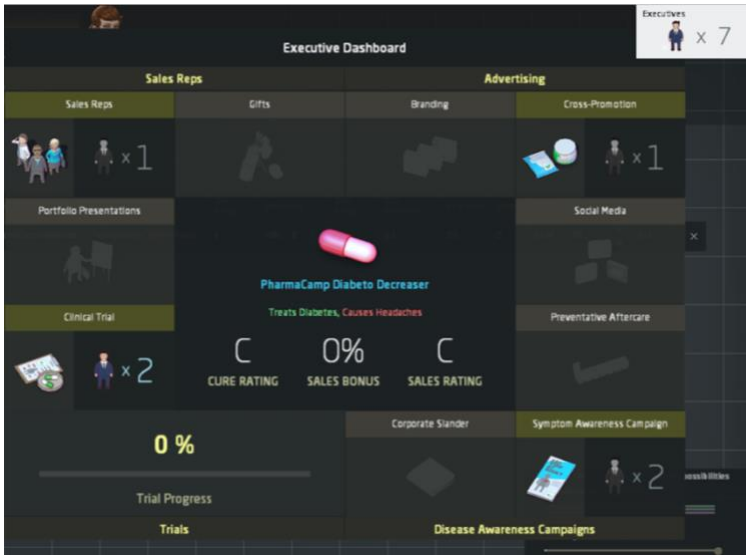

Figure S6.6 Representative screen where clinical testing can be selected.

Implementing Tracing - 1 QP

The FDA requires a paper trail for all drugs sold in the US. To make sure you have proper identification of your products use a packer. Click here for a step-by-step example.

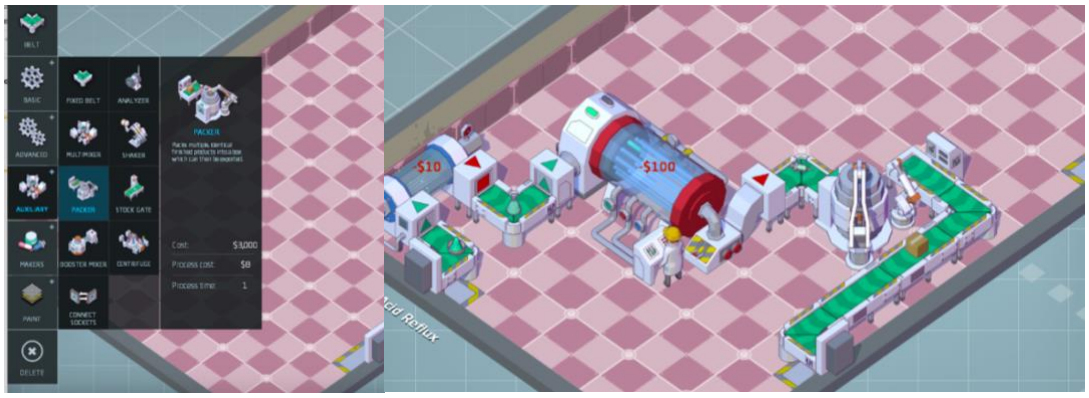

Figure S67. Example of tracing (or serialization). Tracing device present on the left. Tracing device within the process line presented on the right.

Taking Inventory - 1 QP

For quality to be ensured all your products should be accounted for. Use a stock gate on your product lines to conduct inventory. Click here for a step-by-step example.

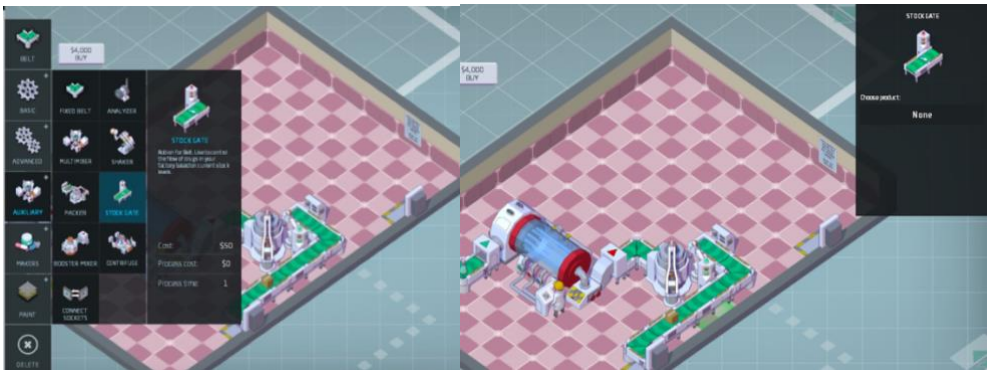

Figure S6.8 Example of taking inventory. Inventory device present on the left. Inventory device within the process line presented on the right.

Continuous Improvement- 1 QP

Upgrade at least one drug to get this QP. Click here for a step-by-step example.

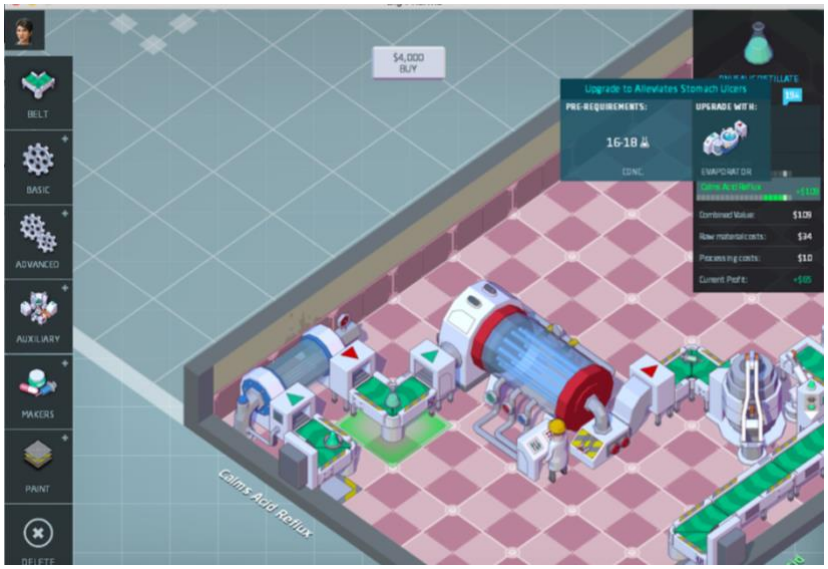

Figure S6.9 Example of continuous improvement.

ETHICAL TIMETABLES

PLAYER T1

Table S6.1 Player T1's ethical timetable for Prompt 1.2.1

Time(minutes)	Type	Notes
9:22	Ethical	Is selling an injectable drug. With tracing. At max concentration. As well as analyzing both ingredients and drugs.
10:08	Ethical	Runs a clinical trial.
12:29	Unethical	Sold capsules. Potent. Without tracing.
13:09	Ethical / Unethical	Starts analyzing capsules.

16:45	Ethical / Unethical	Makes another capsule line. Max concentration with tracing and analyzing.
20:20	Unethical	Deletes injectable process line.
24:48		Takes out loan. Is running into financial trouble.
52:29	Ethical	Player brings back injectable drug. Potent. No tracing.

Note the player did not immediately pay back debts to bank though they could afford too (See Figure S6.10).

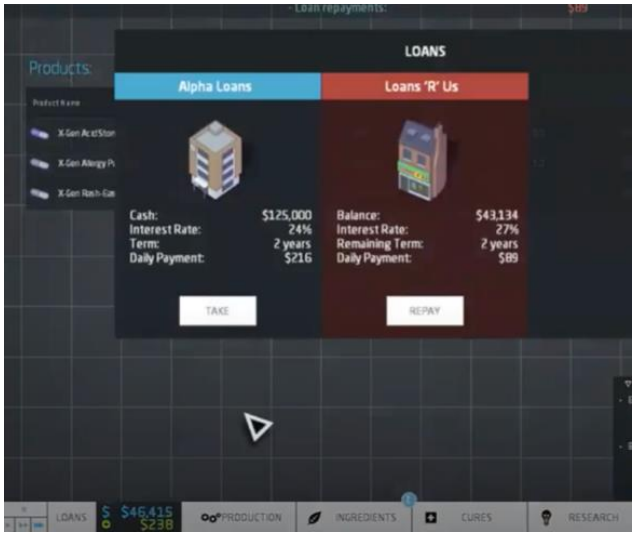

Figure S6.10 Depiction of players time at 44:44 minutes.

Also note Player was in debt when they skipped task 2.

Summary: Starts out selling an injectable at max concentration. Process line had tracing and was analyzing the drugs properly. Before starting a capsule line. The capsules were potent. And the capsule lines typically contained tracing and analyzing. The player struggled to turn a profit regardless and eventually deletes the injectable line entirely. Solely selling capsules the player can turn a profit. Near the end of the game they relaunch the injectable product. But run out of space so they do not implement tracing although an attempt was made. Ethical Score: 2/3

PLAYER T2

Table S6.2 Player T2's ethical timetable for Prompt 1.2.1

Time(minutes)	Type	Notes
3:35	Ethical	Developing a line and analyzing ingredients.
5:55	Ethical / unethical - E	Has an injectable line with tracing and analyzing. Subpotent but in a way that i minimize side effects.

Where an E represents an unethical decision under an expectation.

Summary Player developed an injectable drug. Sold subpotent but in a way to minimize side effects. Ethical Score: 4

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