Protecting Public Health: Unique Identification of Facilities in Adverse Event Reporting

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Sponsoring Agency: United States Food and Drug Administration

Submitted to:

Project Advisor: David DiBiasio, WPI Professor
Project Co-advisor: James Hanlan, WPI Professor
On-Site Liaison: Marni Hall, Director, Regulatory Science Staff, Office of Surveillance & Epidemiology, CDER, FDA

Submitted by:

Joshua Curto, Timothy DeFreitas, Vaughn Walker

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Table of Contents

Table of Figures

Table of Tables

Authorship

Section	Primary Author(s)	Editor(s)
Executive Summary	Josh Curto, Tim DeFreitas	Tim DeFreitas
1. Introduction	All Members	Tim DeFreitas
2. Background	Tim DeFreitas	Vaughn Walker
2.1Brief History of Pharmaceuticals	Josh Curto	Vaughn Walker
2.2 Modern FDA	Josh Curto	Vaughn Walker
2.3 Adverse Event Reporting	Tim DeFreitas	Josh Curto
2.4 Problems with AER	Tim DeFreitas	Josh Curto
2.5 Unique Facility Identifiers	Tim DeFreitas	Tim DeFreitas
2.5.1 DUNS	Vaughn Walker	Tim DeFreitas
2.5.2 FEI	Tim DeFreitas	Josh Curto
2.5.3 NDC	Vaughn Walker	Tim DeFreitas
2.6 Summary	Vaughn Walker	Tim DeFreitas
3. Methodology	Vaughn Walker	Josh Curto
3.1 Existing Identification Systems	All Members	Josh Curto
3.2 DUNS at FDA	Joshua Curto	Tim DeFreitas, Vaughn Walker
3.3 Requirements for responding to Adverse Events	Josh Curto, Tim DeFreitas	Tim DeFreitas, Vaughn Walker
3.4 Gap Analysis	Tim DeFreitas	Josh Curto, Vaughn Walker
3.5 Summary	Vaughn Walker	Tim DeFreitas, Josh Curto
4. Result & Analysis	Vaughn Walker	Tim DeFreitas
4.1 Case Study: Heparin	Tim DeFreitas	Josh Curto
4.2 Adverse Evert Reporting Processes	Vaughn Walker	Josh Curto

4.3 Ideal FDA	Tim DeFreitas	Vaughn Walker
4.4 Bridging the Gap	Tim DeFreitas, Vaughn Walker	Josh Curto
4.4.1 Policy	Vaughn Walker	Josh Curto, Tim DeFreitas
4.4.2 Technology	Tim DeFreitas	Vaughn Walker
4.4.3 Processes	Josh Curto	Tim DeFreitas, Vaughn Walker
4.5 Impact	Tim DeFreitas	Vaughn Walker
5. Conclusions & Recommendations	Tim DeFreitas, Vaughn Walker	Josh Curto
Appendix A	Tim DeFreitas, Josh Curto	Tim DeFreitas, Vaughn Walker
Appendix B	Josh Curto	Vaughn Walker
Appendix C	All Members	All Members

Executive Summary

FDA has a comprehensive but complicated infrastructure for responding to adverse events. The Office of Surveillance and Epidemiology, a division within the Center for Drug Evaluation and Research, maintains FDA's Adverse Event Reporting System (FAERS), as well as extensive product and manufacturer dictionaries. When an adverse event occurs, a patient, healthcare professional, or company submits an event report to FDA and a record is entered into FAERS. Safety evaluators are then responsible for searching through FAERS for patterns and signals that may be threats to public health. However, locating facility-specific information within the system is often challenging. In cases like the New England Compounding Center meningitis outbreak of 2012, this lack of information can have disastrous results. FDA has expressed the need for a better system to link events and manufacturer information in order to more quickly detect and respond to public health issues.

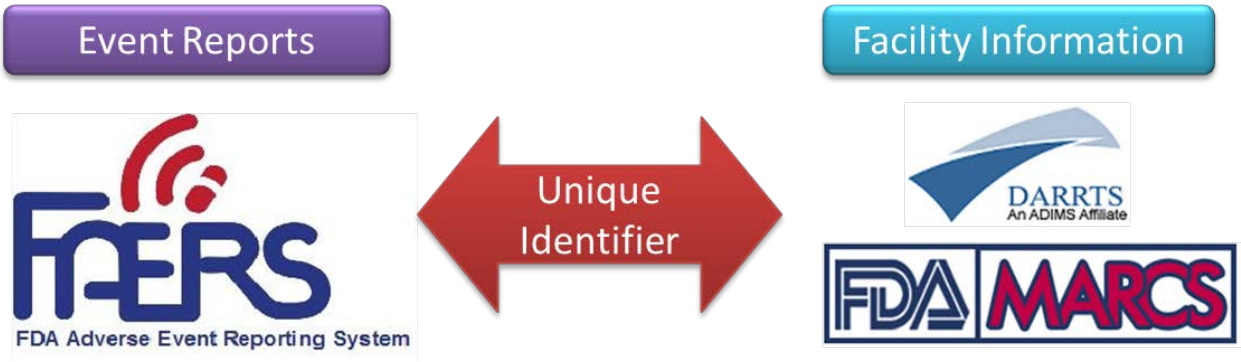

Figure 1 – Overview of the project. This project provides recommendations on the use of unique identifiers to link FDA facility databases with adverse event reports.

The goal of this project was to provide FDA with recommendations on the introduction of a Unique Facility Identifier (UFI) within the adverse event reporting system (Figure 1). We conducted a series of interviews within FDA offices to determine the primary needs of regulators as they relate to facility information, and identified common obstacles encountered during

investigations. During these interviews, we also identified that two UFIs (DUNS and FEI) are already in use within FDA. Using a variety of case studies obtained from previous FDA investigations, we have highlighted the strengths and weaknesses of existing systems, and used case studies from safety evaluators to propose an ideal state of FDA. We then developed a series of recommendations for changes to FDA policy, informatics, and processes based on a comprehensive gap analysis including implementation challenges and backwards compatibility.

This project has found strengths and weaknesses of both DUNS and FEI numbers, but observed the need to migrate towards a single UFI. We recommend the direct association of a UFI with adverse reports submitted as part of FDA's future adverse event reporting system. FDA should provide short term guidances to industry recommending the inclusion of a UFI as part of mandatory reporting, eventually requiring UFI submission with regulation. With a UFI associated with event reports, FDA can develop tools and processes to support the link between reporting and facility information, thus minimizing the costly manual detective work of today's safety evaluators.

1. Introduction

Consumption of pharmaceuticals has increased rapidly worldwide over the last century. According to the International Federation of Pharmaceutical Manufacturers & Associations (2012) annual pharmaceutical sales in the United States alone has reached 337.1 billion dollars. Although the amount of money spent on pharmaceuticals is substantial, proving that a drug is safe for public use is difficult and time consuming. In 2011, only 37 new biological and chemical entities were approved for public use, while over 4,000 were still in development (PhRMA, 2013a).The development of medications is a lengthy process, between 10 and 15 years long (PhRMA, 2013b), full of roadblocks and regulations to ensure that approved drugs are safe, pure and effective. In the United States, this process is regulated by the Food and Drug Administration (FDA).

No matter how thorough FDA's approval process is, there are still a variety of problems that arise related to a drug's use and distribution. Problems can range from mislabeling to unexpected reactions to a drug, both of which are serious safety concerns (FDA, 2013c). The faster FDA can respond to these events, the greater the probability of avoiding large-scale public health disasters like the New England Compounding Center meningitis outbreak of 2012. In the ideal case FDA must respond with appropriate regulatory action the minute an adverse event occurs. But due to the large number of adverse event reports (more than 1 million per year) and inconsistencies in the data received, reacting quickly is incredibly difficult.

FDA's current solution is a complex database known as FDA Adverse Event Reporting System (FAERS). FAERS is a system whereby healthcare professionals, manufacturers, and the public can submit adverse event reports electronically to a centralized database, where they can

be analyzed by FDA. The system is not without its problems (Auerbach, 2012). FAERS does not require that an event be a direct result of a prescribed drug as some foreign systems do (Morris, 2012), and as a result it can be difficult to identify true drug events amidst the background health problems occurring randomly. This problem is often compounded by the lack of manufacturer or distribution information about the drug involved and further by the lack of consistent naming conventions. FDA must be able to identify related events, i.e. those with the same drug, manufacturer, and reported symptoms, in order to detect signals amidst the large number of reports received. But because identical manufacturers and events may be labeled differently within the database, no one query or drug name may reveal the information necessary, and the response time increases. As many of these problems have long been considered intractable, the only way for FDA to improve response time has so far been to hire additional personnel.

Yet, there are few studies that examine the possibility of altering the database or reporting structure itself (Auerbach, 2012). Using a unique facility identifier (UFI), a number which is specific to one facility that could be used as a reference in a database, would solve the naming problem by linking drugs directly to its manufacturer's UFI in an event report. UFIs are used elsewhere at FDA to track inspections, but have not yet been used within adverse event reporting. One such identifier, the Data Universal Numbering System (DUNS) is widely used throughout the US government for contracting and by Compliance at FDA. DUNS numbers are hierarchical, meaning FDA could quickly relate events to a particular company or manufacturer. Other potential systems include FDA Establishment Identifier (FEI), National Drug Code (NDC), and New Drug Application (NDA), and each has its own benefits and drawbacks. It is not yet known whether using a UFI would solve the underlying problem of incomplete data or provide a tangible improvement to response time for adverse events.

The goal of this project was to evaluate the current use of identification systems within FDA, and assess the addition of unique identifiers such as DUNS number in adverse event reporting as a means to improve the availability of facility information in pharmacovigilance. Our research began by identifying the unique identifiers used in FDA databases and tools used, analyzing the ability of each to index manufacturing information. By interviewing FDA investigators and determining the information needed to respond to adverse events, we then developed ideal use-cases for safety evaluators with respect to manufacturer information. We then provided recommendations for the future development of FAERS, including discussions of the opportunities and obstacles involved in associating reports with a unique identifier. Improving FDA's complex adverse event reporting system will help to decrease response time, and hopefully save the lives of consumers.

2. Background

This chapter summarizes the development of post-approval regulatory activities of consumer drugs, both in the United States and abroad. These activities are referred to in the pharmaceutical industry as pharmacovigilance, and are the primary responsibilities of FDA and similar agencies. Beginning with the history of drug regulation within the United States, we summarize the challenges of protecting the public's health, and the reasons for developing a drug adverse event reporting system. Because the current systems are imperfect and have severe limitations, including the response time and veracity of information, FDA has proposed the incorporation of a unique facility identifier into their data storage system. We describe the details of the facility identifiers and summarize the anticipated challenges of implementing such a system on top of FDA's existing programs.

2.1 A Brief History of Pharmaceuticals

Since the Middle Ages, apothecaries and other medical institutions were needed by the general population. However, the pharmaceutical industry we know today did not begin to appear until late in the 19th century (Walsh, 2010). While the scientific revolution of the 17th century had opened minds to research and experimentation, and the industrial revolution of the 18th century had transformed the production of goods, however, the combination of the two to create the current pharmaceutical industry did not start to appear until the American Civil War.

During the Civil War painkillers and antiseptics were in high demand, which caused many small pharmaceutical companies to move their efforts away from consumer drugs and medicines and toward making the very much needed chemicals for the war effort (Pazzano, 1999). After the war had ended, however, companies returned their primary focus to

pharmaceuticals that could help to improve the health of the public. As the market for medications grew, many companies began producing fake products that caused more harm than good. After US soldiers were poisoned with contaminated Mexican quinine water used for the treatment of malaria, foreign products were put under regulation (Pazzano, 1999). Between 1876 and 1905 over 190 laws were brought before Congress to address the issue of unregulated drug and food products, but not one of them passed. In 1906, Congress passed the Pure Food and Drug Act, which prohibited the manufacture, sale, or transportation of adulterated, misbranded, poisonous, or deleterious foods, drugs, medicines, and liquors, and regulated traffic therein, and for other purposes (Bethesda, 2004, p.768). The Act fell under the Bureau of Chemistry a branch of the Department of Agriculture. This Act became the foundation for what would later become the Food and Drug Administration.

In 1906 Dr. Harvey Wiley became the chief enforcer of this new act and began working with a group of young scientists to analyze the safety of the vast number of products now available to the public (Compliance Media, 2008). As Wiley began his work, however, he realized that they needed to have policing power over these industries in order to properly deal with the growing number of fraudulent products. This stance caused Wiley to gain a great number of enemies within the agricultural and pharmaceutical industries and eventually led to his resignation in 1914.

Ten years later, Walter Campbell was put in charge of a task force to assess the effect of consumer chemicals on the public (Pazzano, 1999). His assignment as Chief Commissioner was due to the help of two authors, Stuart Chase and F.J. Schlink, who had exposed many counterfeit cosmetic products, one being tetrachloride and its use as a grease dissolver, insecticide, and bath salt. The public's exposure to these problems forced Congress to create the Food, Drug and

Insecticide Administration (FDIA) in 1927, which became the Food and Drug Administration in 1931. The creation of this administration was a topic of debate for a while, until 1937 when Massengill distributed an Elixir Sulfanilamide, a “cure for strep”, that contained diethylene glycol, which is more commonly known as antifreeze. This caused the death of 107 children, and brought to light the extreme need for the regulation of all food and drug products (Society of Toxicology, 2013). The problem of spurious, falsified, falsely-labeled, or counterfeit (SFFC) medicine persists to this day (WHO, 2012). The extent of SFFC distribution is impossible to determine exactly but is estimated at around 10% of the global drug trade, and almost all types of over-the-counter and prescription drugs have been counterfeited (Swaminath, 2008).

2.2 The Modern FDA

Since 1937, FDA has grown in both size and numbers, and is now in charge of regulating many different products. FDA (2012) has a part in regulating the following products:

- Foods
- Human Prescription and Non-prescription Drugs
- Vaccines, Blood Products, and Other Biologics
- Medical Devices
- Electronic Products
- Cosmetics
- Veterinary Products
- Tobacco Products

To ensure public health is not at risk, FDA has an office that deals with some of these products individually. These offices range from the Center of Veterinary Medicine to the Office of Medical Products and Tobacco, and each has a list of regulatory actions that every manufacturer must take.

2.2.1 Premarket Regulation: Receiving FDA Approval

When a company develops a chemical compound that it would like to sell as a pharmaceutical to the public, it must first gain approval through FDA. In almost all modern pharmaceuticals, (the first step is animal testing (FDA, 2013a). This is done on a range of species to determine toxicity, and effectiveness of the compound. After that process is complete, the company files an Investigational New Drug application (IND), which reveals the outcomes of the initial animal trials and outlines what the company proposes for human testing in clinical trials. When FDA receives the IND, the main purpose is to make sure that human trials would not put anyone at high risk, and to ensure adequate human consent and protection.

Once approved for clinical trials, the drug enters Phase I, which typically contains between 20-100 people with the focus being on major side effects and metabolization of the drug (Demets, 2010). If successful, then the drug enters Phase II (100-300 people), where the goal is to determine if the drug can be effective in people with certain diseases and conditions; these tests may contain a placebo. After the completion of Phase II, FDA and the company decide how large-scale the trial should be for Phase III, which can involve up to 3000 people. Phase III is used to evaluate large-scale safety and dosages, in addition to testing the drug's efficacy in combination with other pharmaceutical products. Figure 2 gives an overview of the timeline for clinical trials.

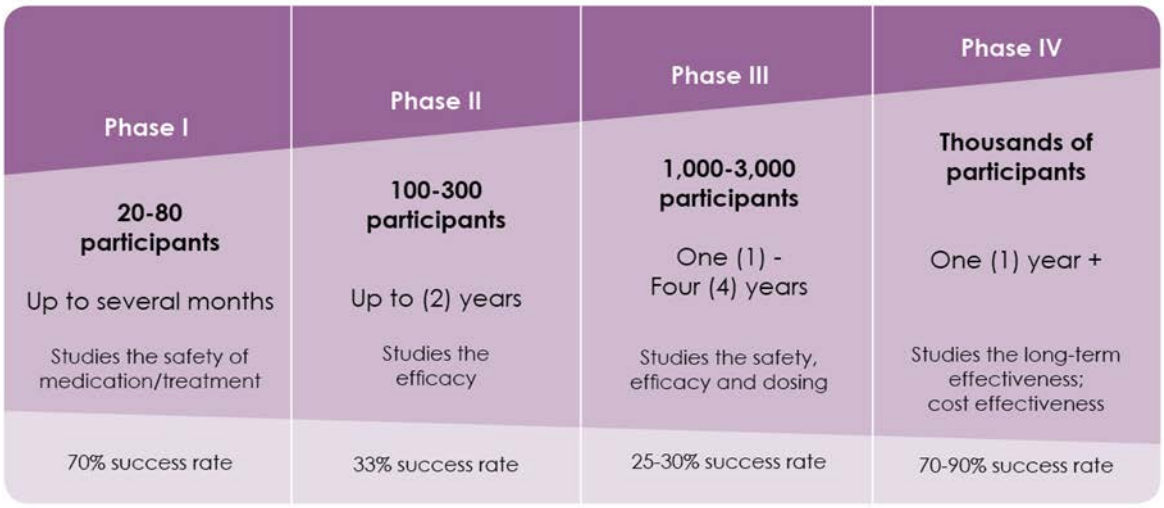

Figure 2 - Timeline for Clinical Trials (CERN, 2013)

If the drug is determined a success through Phase III trials, there is a review held between the drug company and FDA, and a New Drug Application (NDA) is submitted (Demets, 2010). The NDA contains the data analysis of both human and animal trials, as well as how the drug interacts in the body and how is it manufactured. From there FDA has 60 days to decide whether or not the application should be filed, and if so, a review team is assigned to evaluate the research done by the company.

If the review team finds that the research done is thorough enough, then FDA reviews the labeling of the new drug to ensure that is has all the proper information (FDA, 2013a). The last step is a facility inspection done by FDA, after which full-scale production can begin, and the drug is available for public consumption. Even after proper approval through FDA, companies continue to perform and conduct studies on efficacy (Phase IV trials) and are required to submit periodic safety reports on the drug. This is to guarantee that there are no unseen side effects that would warrant a recall.

2.2.2 Postmarket Regulation

When a new drug moves from a control group of 3000 people to the general population, unseen side effects can occur. These side effects can range from a mild rash to even death. These are problems that have to be dealt with extremely fast and efficiently in order to prevent any more harm to consumers. The Center for Drug Evaluation and Research (CDER) is in charge of monitoring pharmaceutical products after release to the public. Within CDER, there are multiple offices that are assigned with different tasks and responsibilities. One of these offices, The Office of Surveillance and Epidemiology (OSE), evaluates the safety profiles of drugs available to consumers in the United Stated using a variety of databases, forms, and other methods of information capturing throughout the life cycle of the drugs. OSE identifies adverse events that are related to side effects that were not present during drug development process. They do this by maintaining a system of postmarket surveillance and risk assessment programs like FAERS. OSE gains information about adverse events through mandatory reporting by companies and voluntary reports submitted by consumers through FDA's MedWatch program, which now total more than one million reports per year. These reports are then stored in FAERS, and monitored by Safety Evaluators to see if patterns or certain events are cause for investigation. Staff in the Office of Surveillance and Epidemiology uses this information to identify drug safety concerns and also to recommend actions to improve product safety. Some of these recommended actions include: updating drug labeling, providing more information to the community on a certain product, implementing or revising a risk management program, or reevaluating approval or marketing decisions.

The Office of Compliance ensures that over-the-counter and prescription drugs are of high quality, properly labeled, safe, pure, and meet applicable drug approval requirements. They

address public health risks and advise the center director on regulatory and enforcement issues involving human drugs. Some of their primary projects include:

- Developing and overseeing drug compliance programs designed to reduce consumer exposure to risks of unsafe and ineffective drugs.
- Monitoring the quality of human drugs through inspectional coverage, product testing, and other pre- and post-market surveillance activities.
- Ensuring uniform interpretation of standards that achieve high product quality through application of current good manufacturing practice requirements.
- Coordinating evaluation and classification of drug recalls and working with field offices for implementation of recalls.
- Implementing programs and projects to identify, assess, and prioritize the public health significance of legal violations.

Although Compliance and OSE both deal with adverse events, they focus on two different types of problems that can arise with drug products. OSE focuses on human side effects and reactions that were not prevalent during drug approval, while Compliance focuses on problems that arise due to poor manufacturing practices or mislabeling. For example, if a product is meant to be a dark blue pill, but when a consumer opens the bottle the pill is light blue; this would fall under Compliance's jurisdiction. However, once the consumer ingests the defective product, and they have an adverse reaction to it, then the report would be filed under OSE.

Another office that deals with post market regulation, that is not a part of CDER, is Office of Regulatory Affairs (ORA). The ORA is the lead office of all agency field activity. They inspect regulated products and manufacturers, conduct sample analyses of products, and

review imported products offered for entry into the United States. They are run by Associate Commissioner Dara Corrigan, J.D. This branch of FDA has at its disposal just over five thousand employees in the fiscal year 2013 (FDA 2013d). Furthermore, the ORA has a budget of approximately 125 million dollars towards activities in the field of Human Drugs in the fiscal year of 2013. This budget is lower than in years past due to a shift in focus of funding along with budget cuts throughout the government.

2.3 Adverse Event Reporting

A drug adverse event is any undesirable experience a patient encounters while taking a drug that may or may not be related to the drug itself (BMA, 2006). It is a less strict form of an adverse drug reaction (ADR), where the cause of the experience is suspected to be related to the drug. The reaction may be a known side effect of the drug, or it may be new and previously unrecognized (MHRA, 2006). Typically these events are submitted by clinicians and healthcare professionals, but most modern systems allow the patient to self-report. Because the scope of clinical trials can never account or control for all side effects of a drug and often suffer from limited sample size and duration of such trials, adverse events are common (Psaty & Strecker, 2004). Since 2003, FDA has received more than 5 million adverse event reports, with more than 900,000 reports in 2012 alone (Figure 3). In order to track and react to trends in response to adverse events, FDA has implement advanced reporting systems such as the FAERS system.

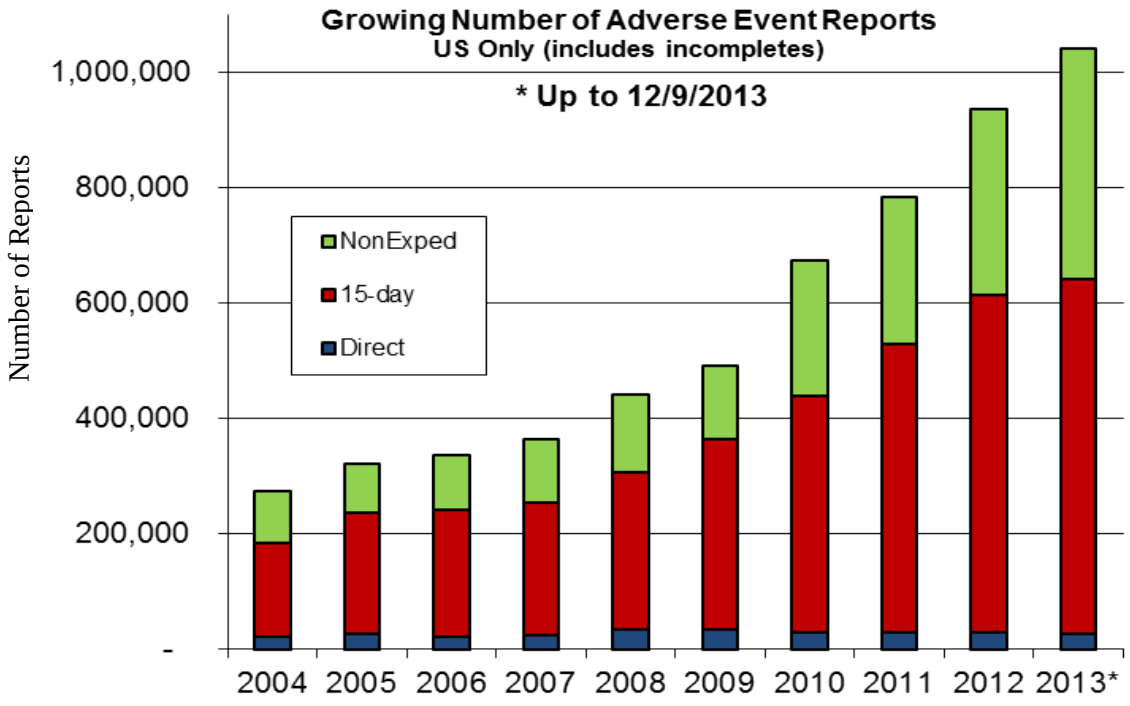

Figure 3 - Adverse Event Reports received per year through Q3 2013 (FDA, 2013b)

Although reporting systems and other pharmacovigilance programs (see 2.3.2) around the world vary in scope and organization, they are over time becoming increasingly harmonized (Faden, 2008). Each regulatory agency shares the common goals of ensuring safe, effective, and high-quality drugs. Companies typically seek approval for their drugs in more than one country, and having similar requirements simplifies the post-marketing demands and improves pharmacovigilance efforts. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2013) is an international project, which recommends standards for systems such as these. Section E2B of the efficacy guidelines summarizes the technical requirements for electronic transmission of reports. In the following section we discuss the major drug regulation systems currently in place in the world and summarize the effects that each has had on public safety.

2.3.1 FDA Adverse Event Reporting System

FDA's Adverse Event Reporting System (FAERS) began in 1998 as a web database designed to store and study safety reports on already marketed drugs (FDA, 2013d). For each event, the system provides empirical data that support FDA's ability to respond to safety concerns, evaluate manufacturer compliance, and respond to requests for information. Reports are evaluated by both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). In the United States, reporting of this information is voluntary. Reports can be submitted to FDA directly through the FAERS website and to manufacturers; all reports delivered to manufacturers are required by law to be forwarded to FDA.

FAERS contains over 7 million reports of adverse events and covers data collected since 1969 (FDA, 2013d). Although FDA is responsible for the safety of the US public, FAERS also receives a few hundred thousand foreign reports each year. The system also tracks patient outcomes, including whether the event was serious or fatal. This information is used to evaluate possible responses, including the collection of more information. Figure 4 shows an outline of how FDA receives and monitors adverse event reports with specific use-cases outlined in chapter 4.

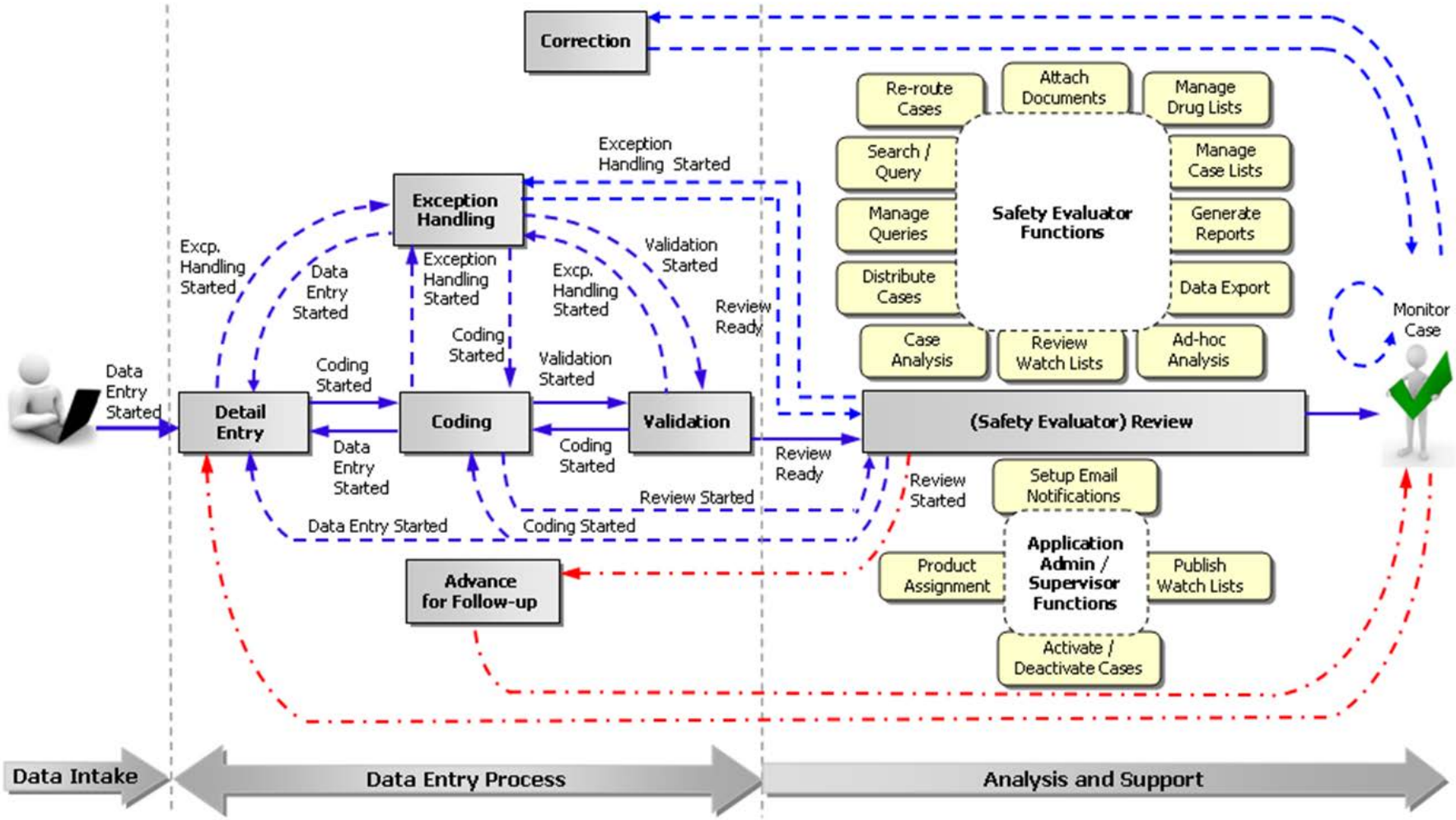

Figure 4 - FAERS workflow. After reports are received, manufacturer and product information is coded against accepted dictionary terms and validated. Once exceptions are handled, the cases are passed along to Safety Evaluators for review. Safety evaluators can then initiate a variety of regulatory functions. (FDA, 2013c)

FAERS is not a perfect system and, like any other, has certain limitations and drawbacks (Auerbach, 2012). The primary drawback is that the system tracks all drug events, regardless of whether a causal link to the drug has been determined. Events can be caused by numerous environmental factors, and there is no guarantee that the event represents a drug-related safety concern. Additionally, reports may not contain enough detail to be able to properly evaluate an event, and FDA does not receive all the reports associated with a given product. As a result, FDA cannot accurately infer the cause of a particular event or medication error in the US.

2.3.2 Other Adverse Event Reporting Systems

There are numerous other reporting systems used in organizations worldwide and in primarily state-run agencies in Europe and Asia. The largest of these is the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance), the European counterpart to the FAERS launched in December of 2001 (EMEA, 2013). It is also compliant with ICH Guidelines, implementing a fully automated message processing mechanism and a large pharmacovigilance database with querying and tracking ability. Like FDA, data entered into the database reflects all events, not just those with a proven causality. To make this even clearer, each report is called a suspected adverse reaction, with an extension for serious unexpected suspected adverse reactions (SUSARs), which occurred during clinical trials. Data from this system is evaluated monthly, with certain drugs evaluated every two weeks. In almost every aspect, this system is similar to FAERS, as both conform to the ICH E2B data standard. The only differences are in how the data are analyzed, which is largely depends on the human resources and front-ends of databases.

Some smaller scale programs include the United Kingdom's Yellow Card program (MHRA, 2013), Japan's Direct Patient Reporting system for Adverse Drug Reactions (Mori,

2012), and the Korean Institute of Drug Safety and Risk Management's ADR system (KIDS, 2013). As noted above, the differences among these systems are relatively minor in an attempt to have cooperative databases. Although each agency may use and analyze the data they receive differently, a majority of these systems conform to the E2B standard, and as a result performs similarly (ICH, 2012). One primary difference between FDA and Yellow Card is that UK reporting guidelines are stricter. In the UK, an event must be confirmed to be drug-related, and as a result, there are fewer data reports received. However, the stricter guidelines for reporting result in more thorough reports with higher quality data (BMJ, 2006).

2.4 Problems with Adverse Event Reporting

FDA's adverse event reporting system is not perfect (Baltazar, 2007). In certain cases, missing or conflicting information regarding patient's health information can result in extended periods of time during which a dangerous drug is still on the market. We briefly describe two instances in which FAERS struggled to effect immediate action by FDA.

2.4.1 NECC Meningitis Outbreak

In October 2012, an outbreak of fungal meningitis was discovered in the United States and was traced to three lots of epidural steroid injections (CDC, 2013). The drugs were distributed by the New England Compounding Center (NECC), and as of July 2013 have resulted in 64 deaths (see Figure 5). FDA was criticized for moving too slowly to react to the crisis, both because NECC had previous safety problems and due to the growing number of meningitis reports (Morgan, 2012). During the subsequent congressional hearing, it was revealed that FDA had received numerous reports over the previous decade but had waited years for any regulatory action. Although in retrospect it seemed obvious (especially to Congress) that there was a problem with the compounding pharmacy, determining trends based solely on adverse

event reports is both a difficult and complex task. Because event reports are not always complete, and manufacturer information is not always available, detecting trends of a few hundred from over a million reports are exceedingly difficult. As a result, the contaminated lots remained on the market for more than 4 months and resulted in more than 750 persistent infections. FDA needs a better way to handle and interrelate the data it receives in order to more quickly identify outbreaks such as these.

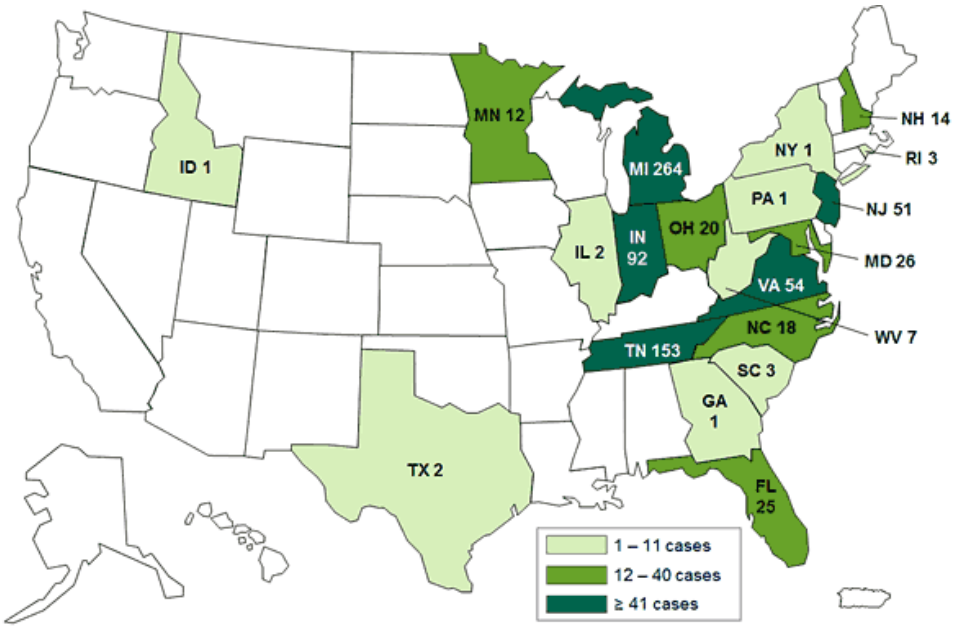

Figure 5 - Cases of fungal meningitis linked to New England Compounding Center as of July, 2013 (CDC, 2013)

2.4.2 Vioxx

Adverse events can also result from unintended side effects of a drug. In 1999, FDA approved Merck & Co.'s nonsteroidal anti-inflammatory drug Rofecoxib, better known by the brand name Vioxx, as a treatment for osteoarthritis and acute joint pain (Bombardier, 2000). However, a number of studies that began during clinical trials and continued over the next 5 years showed that Vioxx increased the risk of heart attacks by 300-500%. FDA estimated that

Vioxx caused between 88,000 and 139,000 heart attacks, of which 30-40% were fatal, before the drug was finally recalled in September of 2004 (Juni, 2004). In this case, the problem was conflict between the results of Merck's clinical trials and the post-market third-party study. The initial experiments showed little cardiovascular risk, some of which may be explained by unethical misrepresentation of data, which were not conclusively refuted for some time. Although adverse events were received, the lack of quality information prevented FDA from definitively identifying Vioxx as the culprit. This problem is exacerbated by the fact that FDA does not require adverse events to establish cause of an event. If FDA can improve the quality of its data retrieval, more significant evidence can be generated to initiate a recall.

2.5 Unique Facility Identifiers

In its current form, FAERS requires only four fields when an event is submitted: patient information, reporting entity, suspected drug(s) involved, and the event code (FDA, 2013b). Each of the other 200 fields specified in the E2B standard are optional, but reports received from industry will also contain the manufacturer name. FDA would like to use this field to trace a drug to a particular manufacturer, but there are certain limitations. One is inconsistent spelling; there are considerable investments made by FDA to maintain a manufacturer dictionary and coding process so that each misspelling can be mapped to a verified name. However, this does not link to a particular facility. In many cases, the exact facility is not known (it may not be on the packaging), so a little extra work must be done to locate the establishment. Below we outline some examples of unique facility identifiers that are used elsewhere at FDA to maintain this granularity

2.5.1 Data Universal Numbering System

The Data Universal Numbering System, also known as DUNS, was created in 1963 by the company Dun & Bradstreet (D&B) to aid in their creation of credit reports (Dun & Bradstreet, 2013). The DUNS system was much better than the system that was in place previously to access pertinent company information. The DUNS system achieved its success by assigning each individual business entity a unique, nine-digit number, which corresponds to the business's information within the D&B database. Dun & Bradstreet's database links each unique business identifier to its parent company and branches using its proprietary software, allowing hierarchies to be viewed (see Figure 6). The DUNS system is widely used throughout the world for tracking business relationships, most notably by the European Commission, the United Nations, and the US government. The US government specifically requires a business to have a DUNS number in order to receive a government contract or grant.

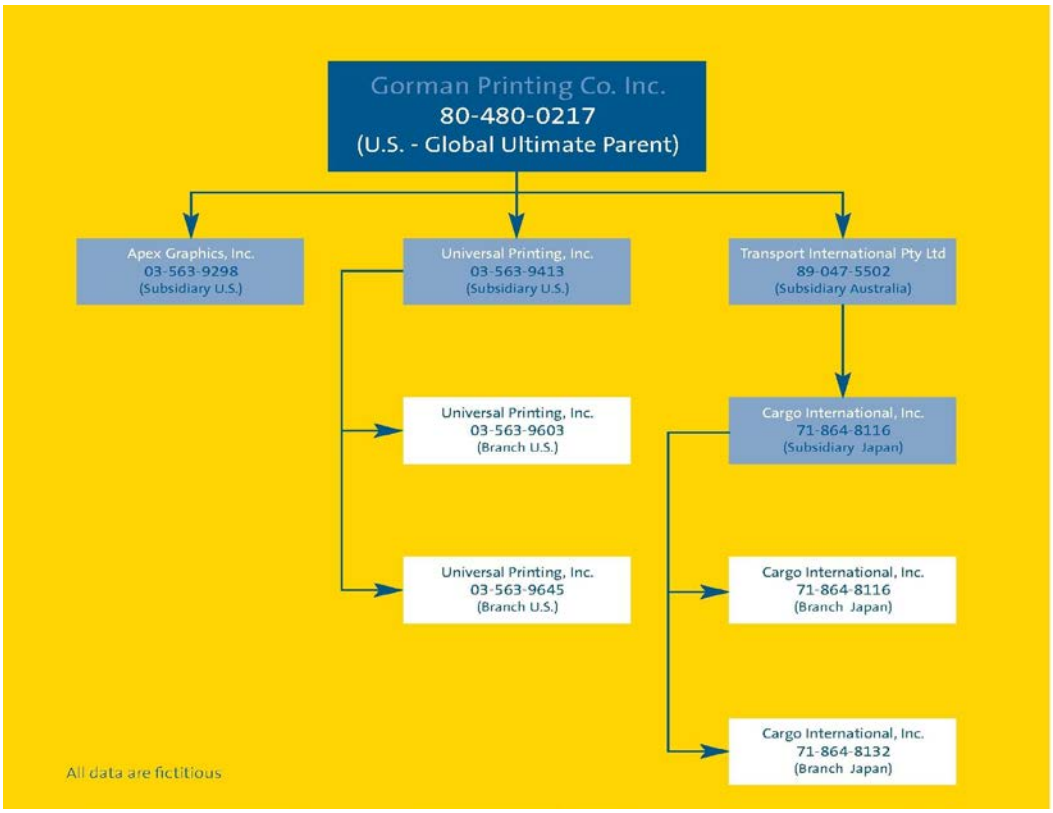

Figure 6 - Example DUNS hierarchy maintained by Dun & Bradstreet (Dun & Bradstreet, 2013)

Each DUNS number is site-specific, which means each separate branch or location within an organization will be assigned a different number (Dun & Bradstreet, 2013). Some businesses use a DUNS +4 system, which allows them to have subsections under their main DUNS number. However, the extra four digits are not assigned by D&B but rather by the business itself. Businesses that have multiple bank accounts at a specific location are more likely to use a DUNS +4 system. Along with the government requirements, DUNS numbers also assist in improving a business' credibility in the marketplace and will help to enable prospective clientele, suppliers and lenders to identify and learn about the business more easily. The corollary in the drug safety space is the ability for FDA to quickly identify the manufacturing site of a particular drug, or perhaps the relationship between raw materials and the drug product. In order to promote more

organized global business, DUNS numbers are either required or recommended by more than fifty global industry and trade organizations such as the European Commission and the UN.

2.5.2 Firm Establishment Identifier

One of the primary internal identifiers at FDA is the 10-digit Firm Establishment Identifier (FEI). FEIs are an extension of the older Central File Numbers (CFNs) that FDA used to register drug manufacturers before 2000. The purpose of these numbers is to facilitate inspections by associating a unique number for each inspection site, thereby allowing FDA to track inspection history, and associate product problems with a location (establishment). An establishment receives a unique FEI when it has one owner and exists in one geographic location, and has been inspected by officials at the Office of Regulatory Affairs. Different buildings on the same campus may have different FEIs, but separate buildings may share an FEI if the activities performed are similar, under the same management, and can be inspected at the same time. These guidelines however, are not codified, and they are interpreted differently at each FDA district office. As with DUNS numbers, FEIs are not changed when a location is renamed or purchased by another company and are not recycled in the event a facility shuts down.

2.5.3 National Drug Code

The National Drug Code (NDC) is a directory of registered drugs that was put into place as a part of The Drug Listing Act of 1972 (FDA 2013f). This act required all registered drug manufacturers to provide FDA with a comprehensive list of all drugs that they manufacture, prepare, propagate, compound, or process for commercial distribution. The drug products listed by manufacturers were identified by their NDC number. The NDC number is a ten digit number

that contains three separate segments used for identification (Figure 7). The first segment is the labeler code which consists of either four or five digits. The labeler code is assigned by FDA and identifies each manufacturer, re-packager, or distributer. The other two segments are not assigned by FDA, but instead by the manufacturer of the drug itself. The second section is the product code and it identifies the exact strength, dosage form (capsule, tablet, liquid, etc.) and formulation of each drug for a manufacturer. The final part of the NDC is the package code which identifies the packaging type and size. All drugs that have been registered for sale in the United States have an NDC number, which is permanent. The way that NDC numbers are normally written is each segment is separated by a hyphen to easily distinguish the different parts. However, this does pose some problems when the NDC numbers are very similar. For example 1234-5678-90 and 12345-678-90 contain the same number sequence but are referring to separate manufacturers and completely different drugs. The NDC number contains vital information about each drug and can be very useful trying to connect drugs to their specific manufacturing location.

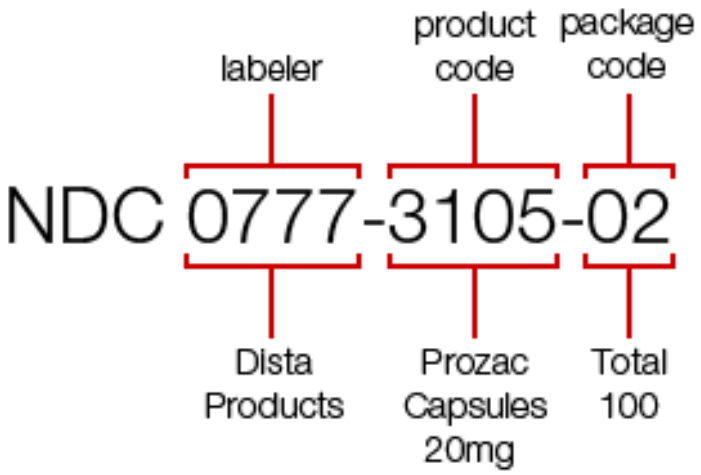

Figure 7 - Embedding of labeler, product, and package code within a National Drug Code number

2.6 Summary

FDA is a very complex organization tasked with an important mission: to protect the health of the public. Under this broad mission falls the regulation of drugs and the reporting of adverse events once drugs are released to the market. Currently, FDA's FAERS system struggles to connect adverse events that are related by their drug's manufacturing site. This lack of connection causes a slower response time between the discovery of a problem and a possible recall, if needed, potentially putting more of the public at risk. The DUNS system has been looked at as a possible solution to this response problem. Allowing the manufacturer information to be easily accessible and stored with other data in a single database will provide a much smoother conversion from an initial problem to regulatory action, such as a recall. Researching the DUNS and similar systems will provide FDA with the necessary information to make a decision about how to improve their current systems.

3. Methods

The goal of this project was to provide recommendations to the Food and Drug Administration on the future development of their adverse event reporting system. We began by exploring the current state of DUNS and other unique identifiers, such as FEI numbers within FDA, and discovered a series of use-cases where FDA can improve. We then examined possible short term and long term improvements to policies, informatics infrastructure, and processes that would result in higher availability of manufacturer information to safety evaluators. We conducted a series of interviews with FDA employees who work with the current reporting system, and got hands-on experience with FDA databases. We used these interviews (using semi-structured protocols, see Appendix C) to collect data on the processes and technologies available, as well as ideal use-cases for obtaining manufacturer information. Using the current state and ideal use cases obtained from the interviews, we analyze and discuss methods of achieving the ideal state of FDA with respect to manufacturer information.

3.1 Existing Identification Systems at FDA

To thoroughly evaluate options for improving pharmacovigilance, we first determined the programs, offices, and data identifiers that are used to track adverse event information at FDA. Safety evaluators within OSE will typically use one or more database and identifier when searching for information. We conducted interviews with these personnel and developed a working knowledge base containing information on usage and implementation for each identifier. This knowledge base was then translated into process maps and visual aids, and was used by the project team as a reference to make informed comparisons between systems. Members of our project team contributed to this reference material via SharePoint, and will

remain archived at FDA. The information we collected allowed us to effectively define what the DUNS and other unique identifiers are capable of before evaluating possible changes. In addition, our research established baseline efficiency of FDA's current adverse event reporting system used in the gap analysis.

3.2 DUNS Numbers at FDA

FDA does not currently use DUNS numbers as part of normal workflow in the Office of Surveillance and Epidemiology. Identifying and interviewing current operators of the databases that use DUNS –such as the Electronic Drug Registration and Listing System (eDRLS) and the Drug Quality Reporting System (DQRS) – gave us a better perspective on its strengths and weaknesses, and has provided us with an understanding of how the system is used. The FDA project team introduced us to the necessary contacts to set up interviews. We collected subjective information on ease of use and current users' perceptions of the system, as well as factual information on the processes where DUNS is used. This supplemented our process maps and knowledge base about existing identifiers and will help OSE become acclimated to DUNS. We also examined the Dun & Bradstreet contract with FDA as part of the gap analysis, because implementation of proprietary information such as DUNS requires explicit agreement with the company.

3.3 Requirements for Responding to Adverse Events

FDA safety evaluators are tasked with overseeing the adverse events they receive and protecting public health. We extended our interviews to determine the information a safety evaluator needs to perform his or her job effectively. Our interview questions focused on the

typical questions an evaluator receives, and the current processes to obtain the answers (see Appendix C). The responses were used to establish a proposed future state of adverse event reporting. We also kept track of problems that safety evaluators encounter during an investigation. Specifically, we determined where information is missing or contradictory, and examined adverse event databases to identify the causes of missing or invalid data. Our analysis examined whether a new identifier would indeed improve the accessibility of manufacturer information, or if the improvements would be minimal because of the poor quality of data received on reports.

3.4 Gap Analysis

After collecting data on current best practices and future processes for obtaining manufacturer information, we examined the changes in policy, technological tools and software, and processes required to bridge the gap. We utilized FDA documents that referenced unique facility identifiers use, and where the agency would like to be in the future. For proper stress-testing, we spoke to employees and picked a case study in safety evaluation that would highlight the effect of specific changes to practices. The 2008 heparin case was chosen because it was a well-known and documented public health event resulting in numerous deaths. It was also chosen because the problem turned out to be site-specific and would have benefitted from the proper linking of manufacturing information. We developed a range of potential changes for a system that captures manufacturing information successfully, and discuss the advantages and challenges of each. Where appropriate, short term temporary measures are also examined. This analysis directly supported our conclusions for the implementation of a UFI within adverse event reporting.

3.5 Summary of Methods

Through the completion of these methods, we have gained the proper information needed to understand the needs of FDA's adverse event reporting system and provide an extensive evaluation of each proposed systems. Through analysis of the current state of FDA, and where FDA would like to be in the future, our team conducted a gap analysis and made recommendations about which system could be most beneficial, along with internal and legislative actions, to facilitate implementation. We presented our research and data to our collaborators at FDA, as well as the Office of Surveillance and Epidemiology, so that they may make informed changes in the future.

4. Results and Analysis

FDA delegates post-market drug regulation across multiple offices, each tasked with a specific area of responsibility. Each office has unique technology and process requirements to organize and store the information relevant to their role, and as a result, they created localized databases tailored to a specific internal need. Each office had not completely considered the impact a particular data standard would have on the work of another office, leading to a chaotic assortment of mismatching facility identifiers. For the inconsistency of these identification numbers caused many problems later on for communication between offices and the agency as a whole.

In recent years, there has been a push for the agency to unify their databases and systems so that they can be mapped to one another, meaning that the databases would communicate with each other and relaying information between them would be much easier and faster (FDA 2009). In 2009, FDA began a shift away from the internal FEI numbers by requiring a DUNS number for drug registration and listing. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) extended the need for FDA to use unique facility identifiers to track imported shipments of pharmaceutical products. Subsequently, in 2013, FDA released a type of formative document called a guidance establishing the DUNS number as the preferred UFI agency-wide. Although there is a movement within FDA to unify and link databases using a UFI as a common data standard, current FDA processes require significant manual translation and analysis. Using heparin as a case study, we examined current challenges and the ideal tools within the reporting universe. We then analyzed the implementation challenges and requirements to meet the ideal.

4.1 Case Study: Heparin

In today's FDA, identifying isolated incidents in the drug supply chain, especially for widely used drugs or generics, requires a thorough investigation and some detective work. Since generics can have dozens of manufacturing sites, an isolated problem might produce only a handful of cases and be hard to detect. Since adverse event reports by their nature do not contain a root cause, FDA tries to observe patterns that might suggest a new problem -- geographic proximity, an abnormally high number of events from one drug, or even a combination of the two. The heparin recall of 2008 highlights much of the detective work that is required in many investigations, and reveals several shortcomings of the data and systems at FDA.

Beginning with a few patients at St. Louis Children's Hospital undergoing dialysis treatment, FDA began receiving reports of nausea, vomiting, and low blood pressure (Lavine, 2009). Initially, these reports were not deemed that unusual. These reports looked like equipment problems related to dialysis, about which FDA receives roughly 40,000 reports per year. Detecting small signals such as the heparin case amidst the large number of background reports is a known challenge at FDA (see Figure 8). The concern, then, was not first identified by FDA, but by the Missouri Department of Health and Senior Services, who contacted the Centers for Disease Control and Prevention (CDC). CDC then sought more information from the dialysis community nationwide, and notified FDA that perhaps Baxter Healthcare's heparin was a possible culprit. But even though FDA had a lead, finding the root cause was still difficult, as each step in the production process could have been contaminated or altered.

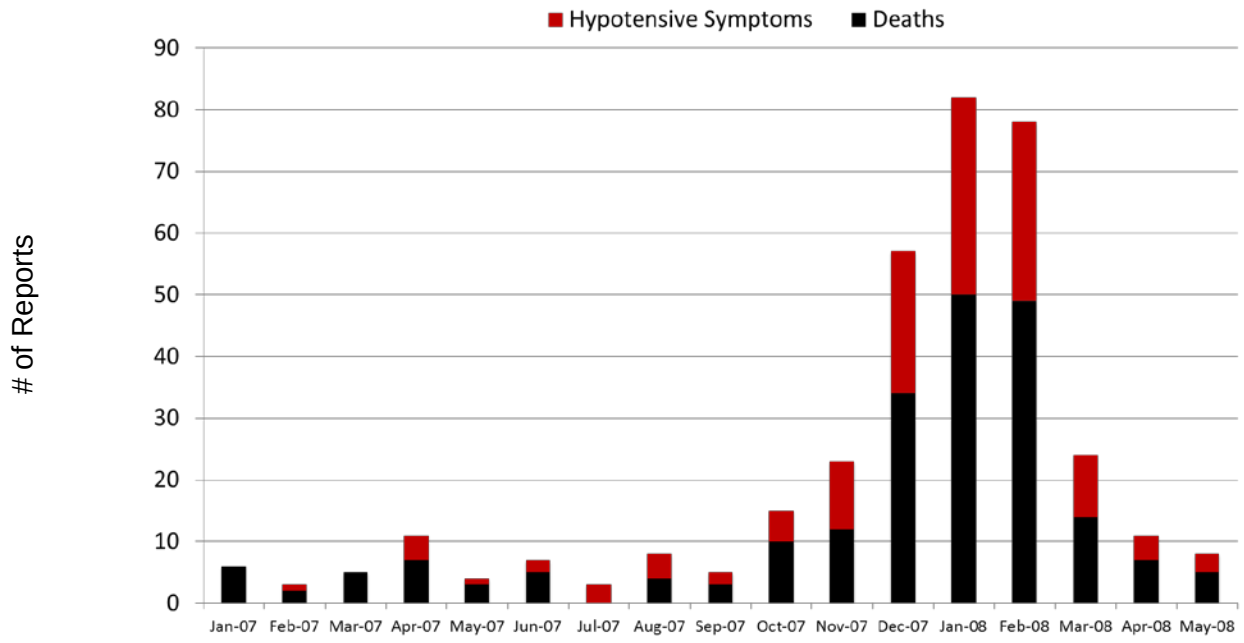

Figure 8 - Heparin cases linked to Baxter recall. Note that the signal was orders of magnitude smaller than the 40,000 background dialysis reports.

Many reports came from multidose vials, which FDA subsequently recalled, but no obvious problem was initially detected by Baxter officials. FDA then reached out to researchers at the Massachusetts Institute of Technology and Rensselaer Polytechnic Institute. They helped identify a foreign substance – over-sulfated chondroitin sulfate, nearly identical to heparin's active ingredient -- in the recalled heparin. It took more weeks to establish biological data proving that the contaminant could cause the reported reactions. Because the contaminant was functionally similar, it seemed that the adulteration was intentional. But for FDA, determining the source of the malpractice remained difficult. Was this an isolated manufacturing incident or common practice? Which part of the production process added the chondroitin sulfate?

From an outsider's perspective, finding the source of this problem should be easy once the contaminated lot is identified. FDA should have information on all the facilities involved in the drug supply chain. However, with generics and foreign drugs especially, this may not be the

case. Eventually, the tainted heparin was traced to Baxter's raw ingredient supplier in China. Although FDA knew that the contaminated lots were linked to Baxter's US manufacturer, this information is not readily available to FDA. FDA does not have the funds to regularly inspect overseas raw ingredient suppliers, nor does it maintain facility information that could be used to quickly identify the source of an outbreak like heparin. Making these connections requires manual detective work and costs valuable time. Each of the processes in the adverse event reporting universe described in the next section can be error prone, and each has room for improvement.

4.2 Unique Identifiers at FDA and Current Adverse Event Reporting Processes

Through our research and interviews with FDA personnel, we were able to assess where each unique identifier is currently used and how it benefits its current system. An overview of the databases and their key identifiers is given in table 1 below.

Table 1 – Overview of databases and unique identifiers in the adverse event reporting universe.

Name	Description	Key Identifiers	Owned by
FDA Adverse Event Reporting System (FAERS)	Stores adverse event reports received through MedWatch and from manufacturers.	MedDRA code, Manufacturer Name, Product Name	CDER/OSE
Drug Registration and Listing (DRLS)	Stores registrations of companies permitted to sell drugs within the US.	DUNS Number, FEI	CDER/Compliance
FAERS Product Dictionary	Maps common verbatim spellings to FDA-standard names for drug products.	Product Name	CDER/OSE
FAERS Manufacturer Dictionary	Maps common verbatim manufacturer names to FDA-standard manufacturer names.	Manufacturer Name	CDER/OSE
Firm Master Listing System	Contains regulatory information on all registered firms.	FEI	ORA
Drug Quality Reporting System (DQRS)	Captures reports of issues with the manufacturing, packaging, or labeling of drugs.	NDC, FEI	CDER/Compliance

As of June 2009, the FDA requires a company to submit their DUNS number when registering as a manufacturer (FDA, 2009). As mentioned before, the DUNS number can be obtained for free from Dun & Bradstreet. During registration (see Figure 9), the company must submit its address (including GPS coordinates), as well as a list of drugs to be produced at the new facility. The registration information and DUNS numbers are stored in the electronic Drug Registration and Listing System (eDRLS), which replaced the old drug registration and listing system that instead required an FEI.

FDA and Dun and Bradstreet (D&B) have negotiated a multi-million dollar contract with each other in order to streamline drug registration and listing of companies. This contract has three main points: FDA access to D&B DUNS number database, FEI and DUNS linkage and cleanup, and maintaining up-to-date information. The database that FDA has access to contains contact information, a business hierarchy, and a business history report including past FDA information such as recalls and others problems. This information can be found in the database by searching a company's DUNS number, or a company name and location.

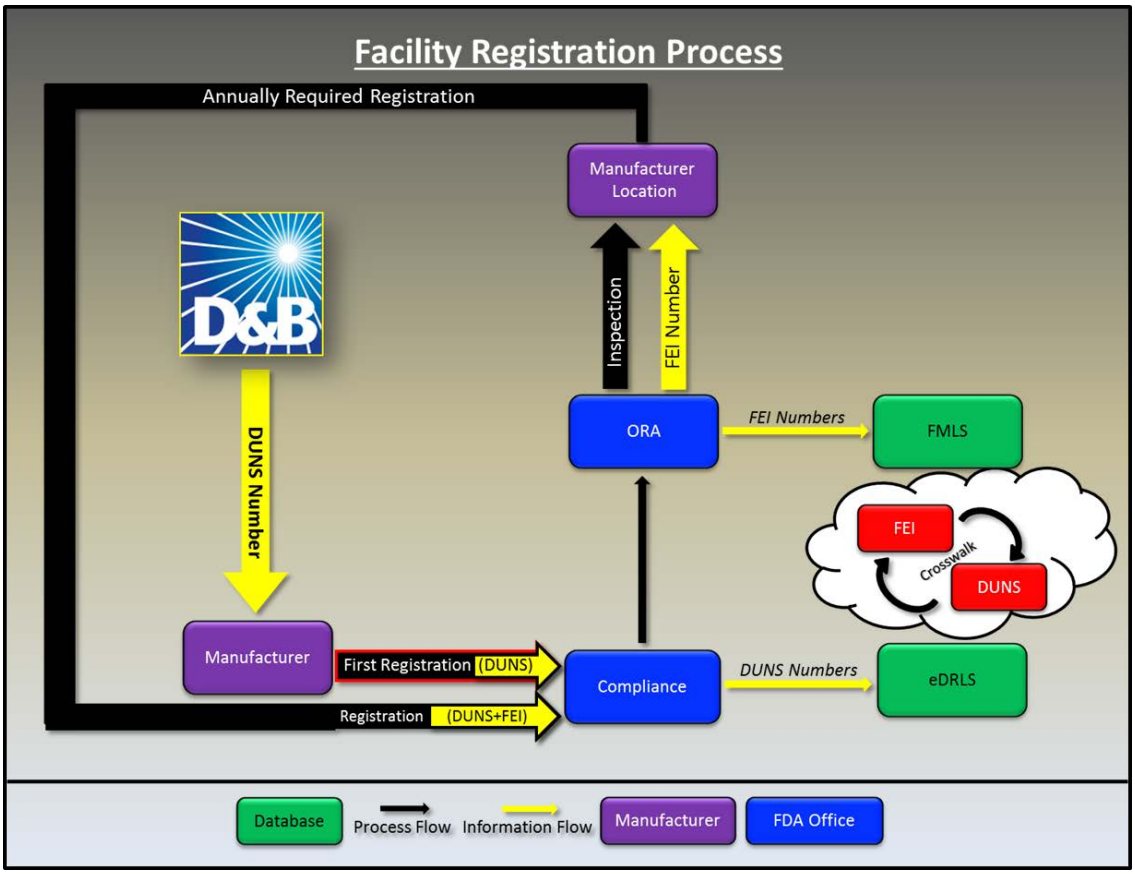

Figure 9 - Facility Registration and the DUNS/FEI Crosswalk

Once a facility has registered with their DUNS number, they must have an ORA inspector visit the site and approve it for whichever processes it may be performing. These inspectors work out of separate district offices that are assigned to certain geographical locations and are responsible for the facilities within their region. Once the site is deemed safe and ready to begin operations, the inspector will assign the site an FEI number, or if it has been inspected before, find the previously assigned FEI. The FEI is then stored in the Firm Master Listing System, or FMLS, within ORA. The FMLS database stores all FEIs and inspection information for ORA. New FEIs are also generated when customs agents cannot link imported drug shipments to an existing FEI when it first reaches US soil. This happens quite often, generating around 10,000 new FEIs per week according to the Office of Information Management. This large influx of new FEIs is why the cleanup and linking of FEI and DUNS numbers is such an

integral part of the D&B contract. FDA sends over 7 million FMLS records monthly to D&B so that they can match FEIs to the 225+ million business entities to which they have assigned DUNS numbers. For example, a company located in Italy had over 30 FEI numbers assigned to a single facility, but with this contract, those numbers are now stored under one DUNS number for that company. This ability to go between FEI and DUNS is referred to as the DUNS/FEI Crosswalk, and has become an essential tool for drug registration.

Once a drug is approved by FDA and receives its NDC number, it is then listed within the eDRLS database. Every drug label is required to have the NDC printed on it, however they are often not reported to FAERS on MedWatch forms. This lack of reporting is because NDC numbers are not a required field on reports and only the consumer can find the NDC on the label, whereas doctors and pharmacists cannot. Relating to the heparin case, with the NDC code available on the tainted drugs, FDA could start the path backwards towards the manufacturer. However, if the NDC code was given on the original adverse event reports, a signal may have been detected much sooner and the problem could have been much less severe. Although NDC is partially linked to manufacturers, the link is not location specific, thus limiting is ability to function as a unique facility identifier.

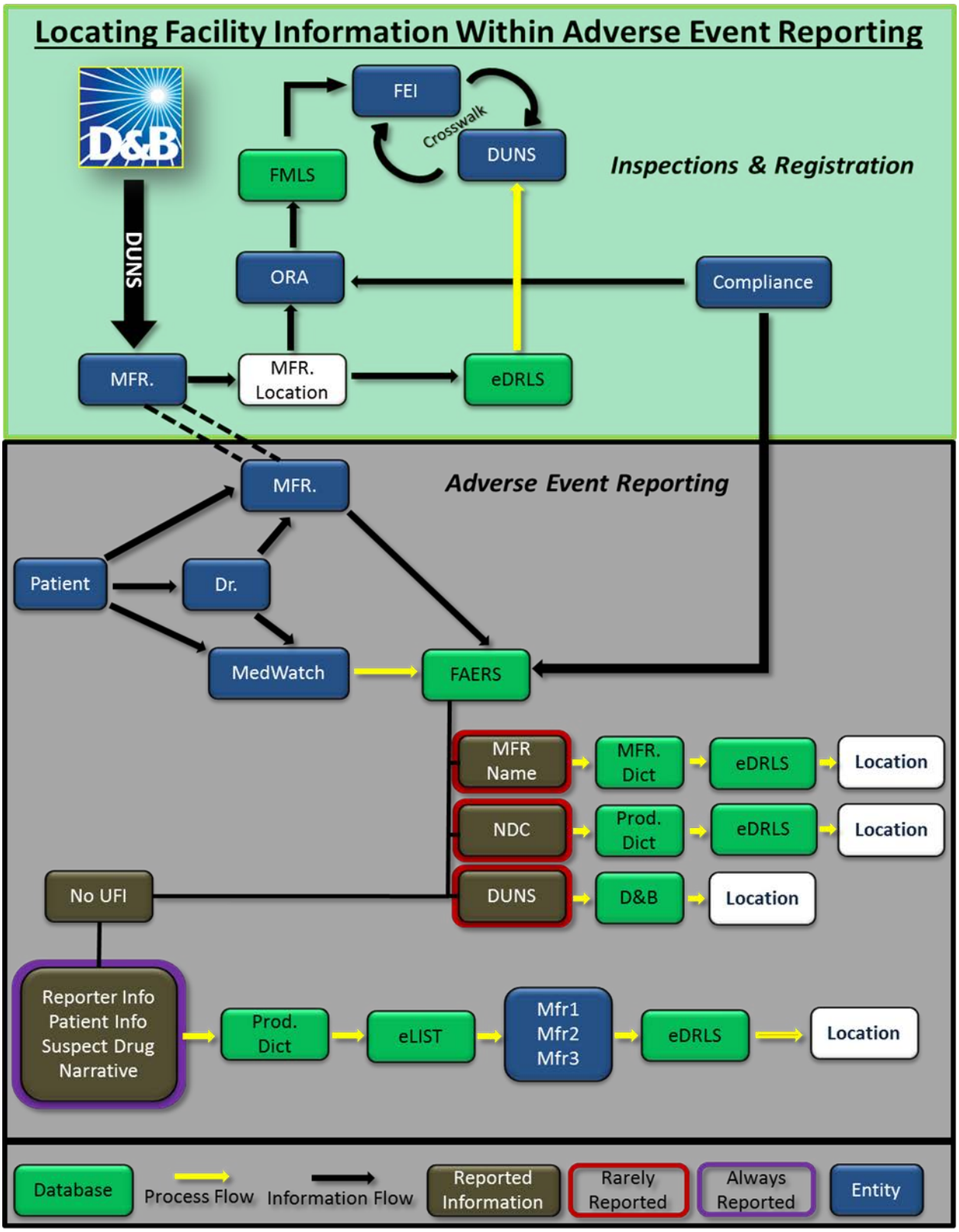

Figure 10 - Processes involved with the exchange of facility information within the Adverse Event Reporting Universe

Using these unique identifiers within adverse event reporting could help with the way manufacturer locations are found (see Figure 10). Currently, when a series of reports is received and a signal is detected, the only information reported is the patient information, reporter information, suspect drug, and an event code, (highlighted in purple on Figure 10). With this information there is a lot of work that needs to be done manually by FDA safety evaluators in order to link the event report to a facility location. The evaluator will take the manufacturer name, if given, verbatim from the report (often there are misspellings) and match it against existing manufacturing sites registered with that name. When there is a misspelling, the verbatim name is coded against the FAERS manufacturer dictionary to find an entry that is a close match. If none can be obtained automatically, the coding process must be done manually. The evaluator will then take the name of the suspect drug verbatim from the report (again there are similar issues with misspellings) and match it to existing sites that are registered to manufacture that drug. Once the evaluator has both the list of sites registered to manufacture the suspect drug and the list of manufacturers with the same name as the report, they can compare the lists to each other and narrow down the field for specific locations that may be the source of the adverse event. However, if the report were to include higher quality data and more specific information, such as an NDC or DUNS number (highlighted in red on Figure 10), the time between signal detection and locating the facility responsible would be significantly decreased.

4.3 Desired Capabilities of the Future FDA

FDA has a number of responsibilities which require locating reliable information quickly. In the ideal case, each FDA database would be linked to one another, with structured and repeatable search functionality for all possible research questions. When an issue arises, and an

investigator needs all of the inspection reports at a given location, there should be exactly one search done that gives the investigator the reports. No time should be spent manually decoding manufacturer names, recovering missing or incorrect data fields, or translating queries between databases. Such efforts are costly, difficult to replicate consistently, and time consuming. Pharmacovigilance at FDA involves more than potential drug problems, and safety evaluators will typically look at a variety of sources in categorizing a signal. In addition to adverse event reports, safety evaluators look at inspections and product problems to get a better idea of the state of a manufacturer (figure 11). This section discusses a series of use-cases that represent significant improvements on top of current FDA processes.

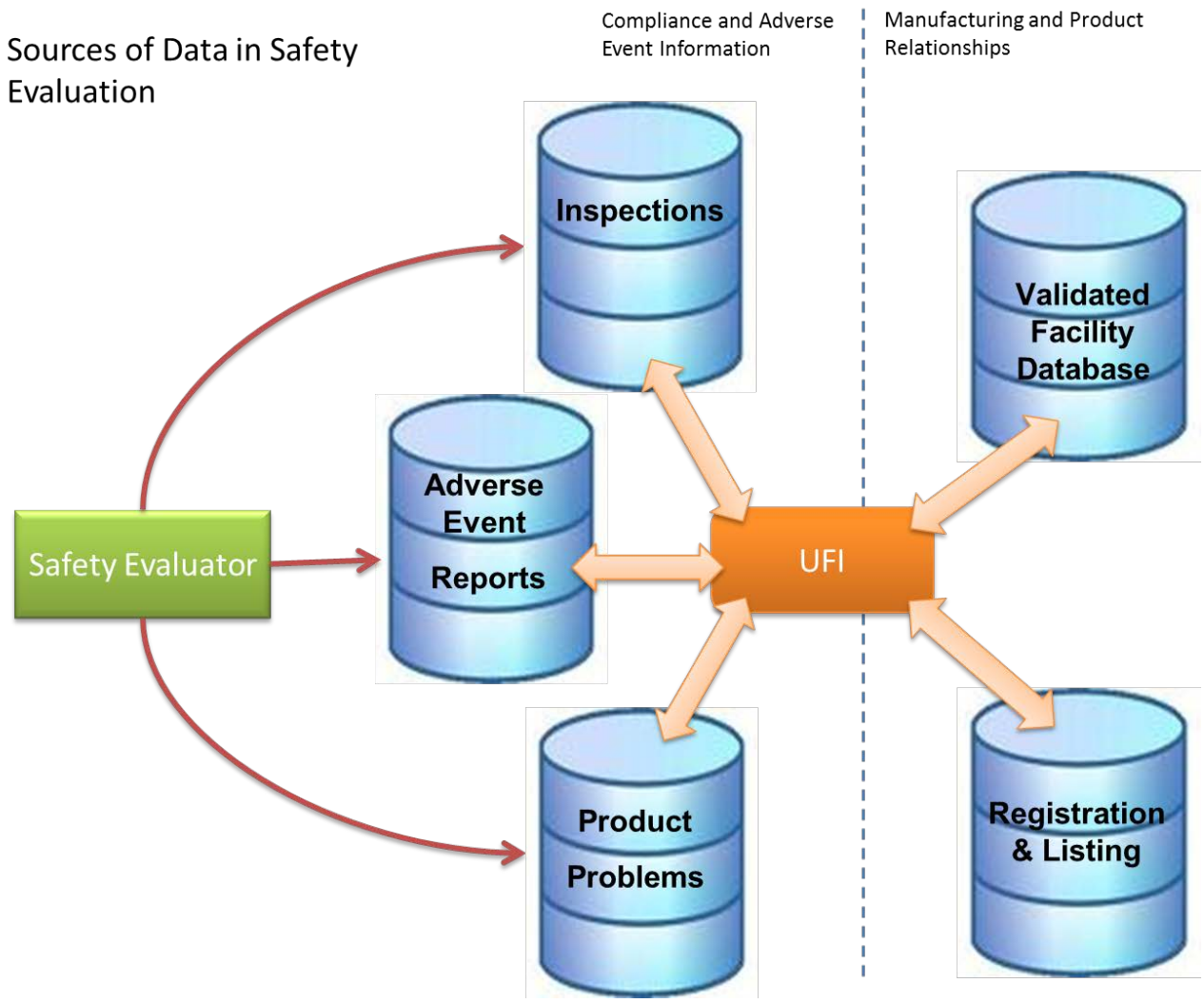

Figure 11 - Sources of data in safety evaluation.

4.3.1 Identification of Manufacturers from Event Reports

An optimal FDA has the ability to automatically associate an adverse event report with a physical manufacturing location and address, as well as any entity in the supply chain that modifies the drug product. In the heparin case, FDA would have benefited from knowing more than just the name of the pharmaceutical company. Each adverse event report should be associated with both Baxter's manufacturing site and the raw materials distributor in China through a unique identifier. Under ideal circumstances once investigators had identified the

heparin signal, they would search through all adverse event reports in database related to heparin, with the ability to list subtotals for events that occurred at specific manufacturing locations and within companies as a whole. This categorization is key: if the reports can be associated with individual manufacturers or manufacturing groups, one can differentially identify a signal as a drug-specific or manufacturing specific-problem. For example, suppose there are established normal levels of heparin reports received by FDA in a given time (table 2). In this example, further suppose that there are two fake companies, each with a set of registered facilities that produce roughly the same amount of heparin. When a report such as the one in table 2 is generated in the absence of a heparin signal, the reports received should have roughly equal numbers of reports from each facility.

Table 2 - Background levels of reports received in the absence of a drug signal. Very rarely are the counts received for any drug zero, even if no unlabeled adverse event is noted.

Manufacturer	DUNS	Location	Reports
ABC Drugs	235647984	Irvine, CA, USA	4
	254677098	Tampa, FL, USA	5
	652856432	Beijing, CHN	4
		TOTAL	**13**
Faux Pharma	086654214	Bern, NC, USA	3
	990876483	Toronto, ON, CA	6
		TOTAL	**9**

However, if there is a significant difference or sudden change is observed between the normal background noise at one facility, then there is strong evidence for a new manufacturing problem at that particular facility, which can then be further investigated (table 3).In contrast, an unexpected number of events could occur that are not related solely to one facility (table 4). In the heparin case, this could be the result of improperly trained doctors or a new combination of procedures and concomitant drugs that would cause reports with all sources of heparin. A query using the same algorithm would show increased reports across all facilities, not just for one

company or location. With the ability to link reports directly to facilities, this could then be cross-referenced with product problems and inspection reports in order to further diagnose the situation.

Table 3 - Example of reports received due to a manufacturing problem. Abnormally high reports are only generated by one facility.

Manufacturer	DUNS	Location	Reports
ABC Drugs	235647984	Irvine, CA, USA	7
	254677098	Tampa, FL, USA	9
	652856432	Beijing, CHN	73
		TOTAL	**89**
Faux Pharma	086654214	Bern, NC, USA	5
	990876483	Toronto, ON, CA	7
		TOTAL	**12**

Table 4 - Example of reports likely unrelated to a manufacturing problem. Abnormally high counts are observed across all facilities

Manufacturer	DUNS	Location	Reports
ABC Drugs	235647984	Irvine, CA, USA	28
	254677098	Tampa, FL, USA	19
	652856432	Beijing, CHN	21
		TOTAL	**68**
Faux Pharma	086654214	Bern, NC, USA	27
	990876483	Toronto, ON, CA	25
		TOTAL	**52**

Similar to the ability to identify all manufacturers from a suspect event, FDA also wants to obtain all relevant reports once a manufacturer is identified. With reports linked to manufacturers through unique identifiers, as in Figure 11, queries linking adverse event and product quality information become simple and routine. Thus FDA obtains a complete overview of the quality of the products coming from a manufacturer. In the heparin case, a number of manufacturer's could have been identified using the querying in the previous section, then an investigator could search for all problems linked to that manufacturer based on its unique identifier. The results would include product problems, as well as compliance and inspection

reports. Compliance may also want to keep track of manufacturers with consistently poor performance, especially those who consistently report adverse events late, who could then be treated differently from a manufacturer with an excellent quality record. This search is complicated, however, by company buyouts and business mergers. In certain cases, a facility that is bought out remains in production of a product, and therefore the inspection history and related adverse events should remain linked. Ideally, a unique identifier provides a permanent solution that obviates the need for searches using frequently changing names. This also aids with backward compatibility; with each report linked to a permanent facility identifier, no information must be altered on an event report or query to locate the entire manufacturer history.

4.4 Bridging the Gap

Linking manufacturer information directly to adverse event reports would require several changes and improvements in policy, technology, and process. Short term measures to increase the availability of manufacturer information rely on the completeness FEI/DUNS Crosswalk and the development of processes or tools to perform cross-database searches. By creating additional linkages, such as between the FAERS manufacturer dictionary and the DUNS numbers in registration and listing, FDA can start to reduce the manual look-ups currently needed. In the long term, direct inclusion of a unique identifier on a FAERS report is feasible and the most technologically reliable solution, although modifications are needed to update current FDA workflow and policies.

4.4.1 Policy Changes for Introduction of a New UFI

Policy change is perhaps one of the most influential ways for FDA to create a change in adverse event reporting. However, being a government organization does not make this process easy. Implementing a change in policy or procedure is a very lengthy and time-consuming

process. Something as little as changing a field on a MedWatch reporting form may seem simple enough but can take years to complete. In order to change an official federal form for any agency, the Office of Business Management (OBM) must approve the form and insure its compliance with governmental and international standards. Since OBM is a separate federal entity, changes that seem essential within FDA may not be seen that way by OBM and other policy makers. Although this process is difficult, there are ways that FDA can implement changes without going through lawmakers. FDA can create a document called a guidance to communicate the best recommended action prior to going into legislation. Guidances strongly urge manufacturers to adopt new practices in order to improve their working relationship with FDA, and so that they can better comply with future FDA legislations.

Although the need for a UFI on adverse event reports is apparent, the policies in place prevent rapid execution. Looking ahead, FDA should begin implementing UFIs within adverse event reporting by to writing a guidance with explicit recommendations for industry to include UFIs when submitting an adverse event report. The reporting of a UFI, such as a DUNS number, should not be difficult for a manufacturer as they should know their DUNS number because it is required for registration and other business related activities. However, requiring the public to submit a DUNS number on a MedWatch report would be impossible due to the difficult nature of finding the number of the involved company. This guidance should also suggest an inclusion of a UFI or sufficient identifier on all drug packaging, allowing the public to be able to report these identifiers. A variety of potential solutions are shown in Figure 12. The simplest options would be to include either the DUNS number or FEI directly. If either is printed on the label, direct reports could easily include the unique identifier and no further look-up would be required, provided there is an accompanying change in electronic submissions and the MedWatch form.

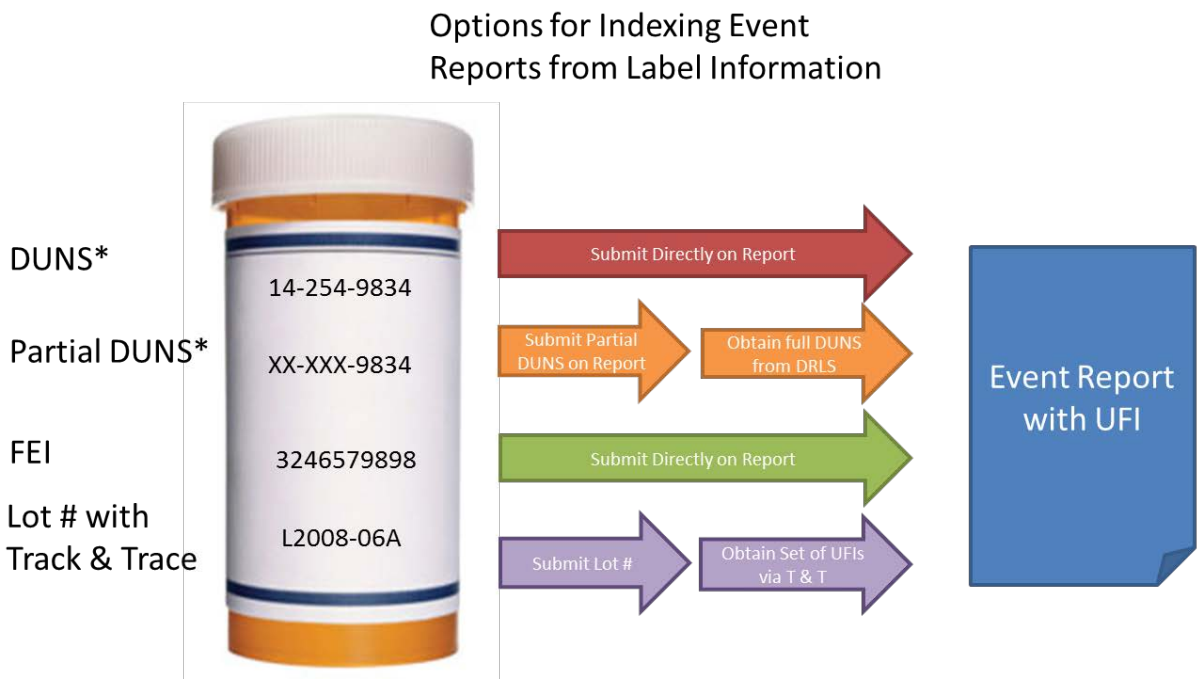

Figure 12 - Options for Indexing Event Reports from Label Information. A variety of possible methods can link label information with a unique identifier. *Requires renegotiation of D&B contract.

However, because the DUNS number is proprietary, printing it on the label currently violates the D&B contract. Dun & Bradstreet do not want the DUNS number available to the public in large quantities, thereby allowing the DUNS number to be used by other companies or individuals to collect that information for possible profits. It might be possible to negotiate a compromise, having a partial DUNS number which could then be verified using the manufacturer and drug name in drug registration and listing in order to obtain the full number. Similarly, a lot number that is linked to a manufacturer through track and trace systems would allow an associated UFI to be obtained prior to its entry into FAERS. This process, once track and trace legislation is implemented, has the additional benefit of tracking multiple facilities. For instance, a drug may receive raw material from one facility, be compounded in another, and then sent to a third facility for final packaging. A track and trace system could associate an identifiers for each with one

number on a report. Regardless of the implementation, adverse event reports would then be linked to a physical location, facilitating the use cases described in 4.3.

Along with the guidance for the inclusion of UFIs on reports from manufacturers, FDA must look at implementing change with regards to data collection and quality. This guidance should raise standards so that reports not containing a UFI would be rejected. From a data collection standpoint, this would mean a significant culture change to FDA, as it emphasizes the quality and usability over the quantity of data received. When FDA began collecting adverse event reports, they wanted as much data as possible, regardless of its quality. This decision was made in a much different environment with regards to reporting than today. Recently, there has been a drastic increase in the number of reports received (refer back to Figure 3), and without standards of data quality, there is a flood of relatively unusable data. However, this proposed guidance would make sure the reports that are received can be assuredly linked to specific manufacturers, and would therefore be more beneficial to an evaluator, as long as each system can use the same identifier. The system, then, relies on an agency-wide decision on the best unique identifier to use, with the two main candidates being DUNS and FEI. A number of arguments as to the right identifier can be made from a policy standpoint.

DUNS has the advantage of a long-standing track record with overseeing contracting with the US government. Dun & Bradstreet are contractually obligated to provide quality data, and are capable of providing several key services related to the DUNS number. The most notable of these is the business hierarchy, an infrastructure which FEIs currently do not support. This means that the company-level collection of DUNS numbers is already complete, simplifying the implementation of a system which can perform the queries listed previously. And because it is

the primary identifier currently in use in drug registration and listing, few policy changes would have to be made to support a move towards DUNS from CDER's perspective.

The DUNS number presents a lot of positive outcomes, but it does pose some challenges (see table 5). An agreement must be reached between Dun & Bradstreet and FDA to allow the mass publishing of a full or partial DUNS number on drug labels and packaging. Additionally, DUNS numbers are not included as part of the international E2B standard. Because E2B is developed by an international committee, FDA could not realistically mandate the inclusion of an identifier specific to an American company. It might be possible, however, that an E2B field be created for a UFI that is not specific to one implementation. Another problem with using the DUNS number is that FDA has limited oversight over the assignment of DUNS numbers, and the information tracked by Dun & Bradstreet. This means that if Dun & Bradstreet were to make a mistake with location information that led to a public health crisis, FDA would still be held responsible. The delegation of work to an outside source can always produce problems that FDA has little control of preventing.

FEIs also meet some, but not all of the goals for an agency-wide UFI. The largest benefit of using FEIs is the main downside to DUNS: FDA owns and assigns them, and they are not limited by a contract to an outside company. FDA can enforce its own internal guidelines and specify exactly how the numbers should be assigned. Thus FDA can define facility at the appropriate granularity, where a DUNS number might not always represent a manufacturing site. In the past however, the numbers have not been consistently assigned, and confusion over proper assignment resulted in facilities receiving more than one FEI. Cleanup of old FEIs has become an involved process. Lastly, because FEIs were created specifically to aid with manufacturing, there is no company-level linkage of FEIs to each other. Aside from registration and listing,

which can use the DUNS numbers to link manufacturers to each other, no direct association can be made between two FEIs without additional informatics solutions.

Table 5 - Summary of advantages and disadvantages of primary unique identifiers

	Advantages	Disadvantages
DUNS	Well-Maintained, Accurate Few Redundant Records D & B Stores Hierarchy	Proprietary Contractual Limitations
FEI	Owned by FDA Highly Specific	Inconsistently Assigned Does Not currently handle mergers, acquisitions

4.4.2 Informatics Improvements for Faster Queries

A shift in policy toward uniting FDA around a common facility identifier would necessitate the creation of new tools and the reorganization of outdated databases. Because a universal identifier eliminates the need for translation between data standards, it should be clear that eventually, all systems storing manufacturer information should share a standard unique identifier. Each search can be keyed using the unique identifier, thus eliminating the need for "fuzzy" searches or near-matches. This goal is ambitious; although FDA has chosen DUNS as the best UFI for registration and listing, decades of information is stored in multiple databases keyed by other fields, most commonly FEI (especially within ORA). Implementation of DUNS would require strategic, incremental improvements so as not to interrupt regulatory ability during the transition away from FEIs. The same would be true for FEIs if FDA reverses the decision to prefer DUNS as the best unique facility identifier.

Before FDA can move entirely towards one UFI, certain tools can be created to ease the transition. One such tool, already in production in the office of information management (OIM), links each FEI to a DUNS number. This tool allows old systems using FEIs to interface with more modern ones like eDRLS, which use DUNS. To emulate the effect of having a system using only one unique identifier, a front-end could be built which translates queries using one system into the other internally, giving results from each database using the DUNS/FEI pair, rather than just one identifier. This system is limited however, in that is impossible to ensure the completeness of results unless the crosswalk accurately links 100% of FEIs. Today, OIM estimates the crosswalk has linked around 65% of the FEIs.

Similarly, until FAERS can include a DUNS-specific field, linkage of the FAERS manufacturer dictionary to DUNS numbers could provide similar functions to the ultimate goal of providing facility information. The challenge of this system is the difference in granularity between a manufacturer name and a unique facility identifier. Whereas FDA uses DUNS and FEIs to refer to a particular facility and geographic location, the manufacturer name may be given only as “Merck”. This can be partially solved by using higher level DUNS numbers -- ones not assigned to manufacturing sites but to the global headquarters of a company-- as shown by the hierarchy in Figure 5. FEIs would not have the ability to assign an FEI to an entire group. This is not necessarily a disadvantage, however, because assigning UFIs to entities other than facilities introduces the same ambiguity that UFIs intend to remove. Once a UFI is selected, coding the name to a DUNS number is easily automated; a manufacturer name should have exactly one number. Through D&B, all the registered manufacturing sites would be linked to this corporate parent, and thus searches for the global DUNS number could produce noisier versions of the same ideal results from searching for one facility’s DUNS number.

A long-term ideal technological solution removes the redundancy between FEIs and DUNS numbers. Using DUNS to maintain business hierarchies allows future FDA technologies to search at different granularities for information. This is especially important in FAERS, where different problems require different sets of data. As with the heparin case above, once an issue is linked to one company, an investigator would like to search for all reports companywide in an effort to characterize the nature of the apparent problem. Using D&B hierarchies, one can obtain a list of the DUNS numbers for each of a company's manufacturing sites. FAERS should be upgraded to allow querying a set of DUNS numbers, resulting in the ability to create tables like the ones in section 4.3.1.

The most important technological improvement is not within any one database, but in the ability for seamless interfacing between all of them. With each system at FDA linked to a DUNS number or FEI, one application could retrieve any and all information about a manufacturer, including FAERS reports, inspections, drug registration and listing. The detective nature of safety evaluation means that determining the root cause of a signal often requires looking in many different databases as described above in Figure 11. Each represents a series of common inquiries which an evaluator would benefit from. The policy section below discusses the feasibility and challenges to such a broad collaborative endeavor.

Another technical obstacle is the ability for the reporting system to receive quality data from the public and manufacturers when they submit a report. As noted above, traditionally FDA desires to collect as much information as possible, yet the information is frequently incomplete or inaccurate. Requiring a UFI to be submitted on a report is only possible if there is a way to collect that information accurately. DUNS numbers are assigned by D&B and are currently not released to the public, yet in order to receive a UFI there must be a way for manufacturers to

identify the facility involved, likely through labelling (refer back to Figure 12). Developing improved reporting forms and user interfaces for submitting the required information might improve the quality and usefulness of the data.

Finally, a novel informatics solution must consciously address backward compatibility issues. If a new adverse event reporting system utilizing unique facility identifiers eventually replaces FAERS, there must be a method for searching the more than 7 million existing records which lack a UFI. Additionally, if systems that use FEIs like DQRS and FMLS switch to the DUNS system, the decades of information must be translated from FEI to DUNS using the crosswalk. Because that data may still be relevant and safety evaluators would still benefit from having access to it, FDA is obligated to maintain access to all of its legacy data.

4.4.3 Process Changes for Offices and Employees

The goals and missions of each office are unique to what their personnel are tasked with, yet there is an overarching theme of protecting public health. However, when an office keeps only its goal in mind, it may not consider the needs other offices might have. Uniting the informatics goals between offices would allow for them to further their missions, and create a stronger collaboration within FDA. Instead of having separate databases, tools, and other office-specific items, there would be open communication between the personnel who work with them about how to increase efficiency and improve them. This communication could be started by creating “working groups”, inter-office teams, which would meet to discuss issues or problems that have arisen concerning databases which are used across multiple offices. One such collaboration that is essential to creating an effective and efficient adverse event reporting system is between CDER and ORA. This collaboration would allow registration and inspections to interact with adverse event reporting, and make manufacturer look up easier in the future.

The newly emerging Office of Pharmaceutical Quality (OPQ) is assigned the task of overseeing the submission reviews, manufacturing facility assessment, and surveillance of the quality of marketed pharmaceutical products. In order for CDER, and more specifically OSE, to gain a properly informed picture of a manufacturer, they must have access not only to previous adverse events, but to past product quality issues as well. This would allow safety evaluators to narrow down their searches based on whether a company is in bad standing with OPQ. Beginning communication between on OPQ and CDER now would allow for faster queries and improved regulation of manufacturers.

One process change that could be implemented would be the requirement of a UFI on reports sent from a manufacturer; however the only office within FDA which can regulate that would be the Office of Compliance. Currently, when a company does not send in reports within the time frame provided by FDA, or they do not meet registration deadlines, then they are contacted, and sometimes fined, by Compliance. If Compliance were to regulate as to whether or not a UFI is put on a report sent by a manufacturer, they would treat a report with no UFI, as if it were a late report. This could be further enforced by Compliance, by rejecting reports with no UFI, therefore pressuring manufacturers into reporting it. This information would then be relayed back through OPQ and CDER, creating the “big picture” of a certain manufacturer, or company.

Currently, upon inspection the ORA field agent would look up a past FEI number or assign a new one if it was not found. With the implementation of a new UFI, ORA would first validate the information with the manufacturer site they are inspecting, then with FDA records. Validation is key to reducing redundancies and incorrect information. This implementation, however, would not include the deletion of previous FEIs that had been assigned to a site. This is due to the fact that the information linked to FEI numbers is still valid and important. The

DUNS/FEI Crosswalk would be a valuable tool for ORA agents to understand which company they are inspecting and how to convey that information to FDA. This process would remove the problem of duplicate UFI's for the same facility, and also increase efficiency of the databases and offices they are stored under.

Once an agency standardized UFI starts being utilized, FDA can begin requiring outside agencies that report to them to use it. Customs plays a big role in foreign pharmaceutical shipping, and is the cause of many duplicate FEIs being assigned. The new process involved would require Customs to verify an address via UFI and report that to FDA. This would stop the creation of 10,000+ FEI numbers a week, and lessen the work done by Customs agents.

4.5 Impact of Proposed Changes

The impact of an agency-wide shift to a single unique identifier with the ability to link all manufacturer information together should not be understated. Although each public health signal is unique, and thus not all investigations will benefit from the proposed infrastructure, a number of real-world benefits can be realized with the ability to obtain this information. In the heparin case, the timeline for initial identification of a manufacturing issue could have been reduced from several months to only a few days or even less. The ability to quickly associate a signal with a particular facility significantly reduces the costs associated with a complete recall. This association also improves the efficiency of FDA of several of the day-to-day regulatory activities. Ensuring product quality and compliance from manufacturers requires consistent monitoring of adverse events, product problems, and inspection reports. With each coded by a unique identifier, searches for information can be automated and replicated consistently, thereby reducing the manual effort in periodically retrieving this data. As long as the integrity and

accuracy of the data can be ensured, processes that previously took hours could take mere minutes.

5. Conclusion & Recommendations

Our research found a notable gap in the ability to associate adverse event reports with compliance information, and vice versa. In many cases, FDA investigations of high-profile recalls were hampered by the inability to access details regarding inspections and the production environments of drugs. After interviews with safety evaluators, it became clear that there is a need for the capability to run searches for event reports at the facility level of granularity, not just at the manufacturer name, in order to produce repeatable and efficient results. By coordinating FDA databases and tools around a single unique identifier, these searches can be easily achieved with limited opportunity for human error using a single application. Only by agreeing to a common identifier can informatics and processes be constructed for efficient querying across the agency. Although FDA has traditionally built projects for a specific purpose within an office, care must be taken to establish agency-wide data standards for common information. The changes suggested by this project are not simple. They reflect significant changes in policy, and will require notable infrastructure investments. Unless the organization of the agency is capable and willing to share information, the proposed technology will never be achievable.

There is no clear winner between DUNS and FEI numbers as to which is most suitable for FDA as a whole. Each office has distinct needs and opinions as to which UFI best fits these requirements. The strengths and weaknesses of each identifier must be carefully considered and discussed between all offices before any decisions are made. Immediate action towards improving adverse event reporting can be taken by forming working groups to share access to pertinent information such as the DUNS/FEI Crosswalk. The migration towards a single UFI will ultimately result in improved efficiency and sharing of data across the agency, but not before the specific data requirements for each office are outlined and discussed.

Many of the problems identified in this project are excellent opportunities for future undergraduate research projects at Worcester Polytechnic Institute. Junior-level projects are required to address aspects of science and engineering within society (see appendix B), a good match for the public health mission of FDA. In addition to social science projects and basic feasibility studies suitable for Juniors, Seniors undertake projects to demonstrate proficiency in their major areas of research. Any of the software tools described above, as well as upgrades to existing FDA databases could be achieved through collaborations with Computer Science students at WPI. WPI's focus on big data solutions could bring refreshing technological insight and improve the accessibility of FDA's considerably large databases. Looking ahead, there are many opportunities for FDA and WPI to collaborate and have successful projects, improving both the FDA and the students themselves.

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Appendix A - The United States Food & Drug Administration (FDA)

A.1 FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and other products (FDA, 2013a). FDA is also active in developing medical devices and has a distinct interest in improving healthcare technology. FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

A.2 FDA and Relationship to this Project

The Food and Drug Administration is a division of the Department of Health and Human Services, and is organized into 8 offices: Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Drug Evaluation and Research, Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, National Center for Toxicological Research, Office of the Commissioner and the Office of Regulatory Affairs (FDA 2013a). Margaret Hamburg is the 21st and current commissioner. FDA is a publicly funded, nonprofit organization, with over 14,000 employees, of whom the majority work in the Office of Regulatory Affairs.

While FDA is the primary regulatory agency for drug adverse events in the United States, there are numerous similar regulatory bodies worldwide. The largest such group, the European Medicine Agency (EMEA) (2013) performs similar duties for the European Union. Additionally,

most developed countries have governmental departments to oversee the safety and efficacy of medicine, such as Japan's Ministry of Health, Labor and Welfare (MHLW) and the Korean Food and Drug administration (KFDA) (2013). Each agency varies slightly in execution and organizational structure, but due to recent and continuing globalization of pharmaceutical companies and the need for cooperation, regulations have become increasingly harmonized (Faden, 2008).

Besides pharmaceuticals, there are a handful of consumer products for which governmental regulation is also mandated. Most manufacturing processes that involve distribution of products to the public are overseen by agencies such as the United States Consumer Product Safety Commission (CPSC). In some cases, however, agencies compete to regulate the same product using different guidelines. The United States Department of Agriculture (USDA), which traditionally oversees packaged meats, vegetables, and fruits, has in some instances competed with FDA (Fuqua, 2011). In situations such as these, competing regulatory models often conflict to the benefit of the company.

To an extent, companies have an incentive to self-regulate and complement the work of FDA. In fact, current FDA policies mandate that the company maintains the responsibility of ensuring a quality product. Although it is common for companies to voluntary recall drugs after adverse events, ensuring a quick response time to the discovery of adverse events requires the use of a federally maintained adverse event reporting system (AERS) (FDA, 2013b). Companies typically do not have the infrastructure to support and track adverse events nationwide; thus the post-market regulation of drugs requires extensive cooperation between patients and health-care professionals who report events and FDA.

Appendix B - The Interactive Qualifying Project

Interactive Qualifying Project (IQP) is typically the major project carried out in a student's third year at WPI. The IQP is mainly an interdisciplinary project (Woods, 2004). Since, most real-world problems of broad scope are, by nature, interdisciplinary, it is important that as part of a technical education, students are exposed to interdisciplinary experiences. Through a student's IQP, they obtain practice in open-ended, unstructured, interdisciplinary problems. They also receive the opportunity to work independently with peers and gain extensive experience in writing about concepts that may be unfamiliar to them. The IQP is the means through which WPI has chosen to make its science and engineering students aware of their professional role in society, and the impact that they may have. The importance of this understanding is reinforced by the proposed ABET Engineering Criteria 2000, which require that engineering programs demonstrate that their students have "the broad education necessary to understand the impact of engineering solutions in a global societal context".

FDA has expressed interest in evaluating a more efficient method of tracking adverse events. Adverse events are major societal issues that FDA hopes to eliminate. However, since that is unrealistic, they are currently working on decreasing the response time between the occurrence of an adverse event and the recall of the drug. This project qualifies as an IQP because it deals with pharmaceuticals which are a product of science and engineering. The main societal problem, however, is drug safety management. The DUNS number is a technological aid that may help improve the response time FDA has to adverse events. In this project we will be examining the interface between the societal impact of drug safety, and the implementation of technology and science.

Appendix C: Interview Protocols

Interview Protocol: Safety Evaluator

Goals of Interview:

- **Understand how a manufacturer look up is currently done**
- **Understand the problems associated with FAERS and other databases**
- **Understand what information is normally given on reports, what is missing, and what is contradictory/useless**
- **Which UFI's are currently in use, and what are the pros and cons of each**

1. Would you like to remain anonymous?
    a. If yes, may we use your job title to present your comments?
    b. If no, record name.

2. Please describe your function at FDA.
    a. What are your responsibilities?
    b. What form does your work take (i.e. writing reports, manufacturer/team meetings)

3. What systems are currently in place that serve as a unique identifier/ number identification system similar to DUNs or FEI?
    a. What purpose to the systems listed serve?
    b. What are the problems with each system?
    c. What is each system best at?

4. What is the current way that the locations or sources of adverse events are determined?
    a. What are the issues with this way of retrieving information?

5. Could a single system meet the needs of all aspects of adverse event reporting?
    a. Would a hybrid system be feasible and/or more effective?

6. What relational capabilities would a system need in order to greatly improve the current way of adverse event and manufacturer linkage?

7. Where do you find necessary information (Databases, Subject Matter Experts, etc.)?
    a. Are these systems/people easy to use/interact with?
    b. How often is data missing/ contradictory/ incorrectly entered?
    c. What do you do when you can't find relevant information?

8. Is there anything else you would like to mention?

Interview Protocol: Data Mining and Signaling Personnel

Goals of Interview:

- **Understand the cause of a signal, use of UFI's, and if manufacturer look up is required**

1. Would you like to remain anonymous?
    a. If yes, may we use your job title to present your comments?
    b. If no, record name.

2. Please describe your function at FDA.
    a. What are your responsibilities?
    b. What form does your work take (i.e. writing reports, manufacturer/team meetings)

3. What information or literature can you provide us with that will help us to become familiar with the way these systems are currently used? (Training and/or demos)

4. When you need information, where do you find it (Databases, Subject Matter Experts, etc.)?
    a. Are these systems/people easy to use/interact with?
    b. How often is data missing/ contradictory/ incorrectly entered?
    c. What do you do when you can't find relevant information?

5. From a data mining stand point, how problematic is a manufacturer look up for you?

6. What types of problems do you encounter due to "low quality data entry"?

7. Are DUNS numbers currently used within the system you work with?

8. What other types of UFIs are in the database currently?

9. Do you think that adding another number would allow for quicker manufacturer look up, or create more of a "mess", or lower quality data?

10. Would adding another identifier make signaling adverse events easier or harder from a data mining perspective

11. Is there anything else you would like to mention?

Interview Protocol: Office of Information Management

Goals of Interview:

- **Understand the extent of the D&B Contract with FDA**
- **Greater knowledge on use of DUNS number throughout FDA**
- **Understand problems associated with DUNS number, and interfacing with current FDA databases**
- **Understand how the DUNS is being linking FEI numbers in the "Crosswalk"**

1. Would you like to remain anonymous?
   a. If yes, may we use your job title to present your comments?
   b. If no, record name.

2. Please describe your function at FDA.
   a. What are your responsibilities?
   b. What form does your work take (i.e. writing reports, manufacturer/team meetings)

3. Which systems are currently in place that use DUNS numbers in their databases?
   a. What purpose to the systems listed serve?
   b. What are the problems with each system?
   c. What is each system best for?

4. What information or literature can you provide us with that will help us to become familiar with the way these systems are currently used? (Training and/or demos)

5. When you need information, where do you find it (Databases, Subject Matter Experts, etc.)?
   a. Are these systems/people easy to use/interact with?
   b. How often is data missing/ contradictory/ incorrectly entered?
   c. What do you do when you can't find relevant information?

6. What is the extent of the capabilities of the DUNS numbering system?
   a. Do these capabilities improve the current state of CDER and/ or ORA?
   b. Would a universal change to DUNS or a similar system be feasible?

7. What is involved within the Dun & Bradstreet contract with FDA?

8. What are problems with the DUNS number, or Dun & Bradstreet that are causing issues with FDA?

Interview Protocol: Compliance

Goal of Interview:

- **Understand how Compliance use UFI's, and what problems they face when using them**
- **Possible suggestions to better streamline the system**
- **If they feel any one of the three UFI's (DUNS, FEI, NDC) would be a useful addition**

1. Would you like to remain anonymous?
    a. If yes, may we use your job title to present your comments?
    b. If no, record name.

2. Please describe your function at FDA.
    a. What are your responsibilities?
    b. What form does your work take (i.e. writing reports, meeting with manufacturers or FDA teams, etc.)
    c. What types of forms, reports, or information do you use often?

3. In Compliance, how often is a manufacturer location needed?
    a. How is a location found if none is given on a report?

4. In your office, what is the main UFI that is utilized, if any?
    a. What are the pros and cons of using this UFI?

5. What information is readily accessible for the person reporting the event?
    a. What information would be difficult for them to find and report?

6. When you need information, where do you find it (Databases, Subject Matter Experts, etc.)?
    a. Are these systems/people easy to use/interact with?
    b. How often is data missing/ contradictory/ incorrectly entered?
    c. What do you do when you can't find relevant information?

7. What information or literature can you provide us with that will help us to become familiar with the way these identification systems are currently used? (Training and/or demos)

8. Do you think that the addition of a new UFI to reports that your office utilizes would be helpful or cause more confusion and room for error?

policy