A Comparative Analysis of Drug Testing and Regulations with a Focus on Antibody Drug Conjugate Approval

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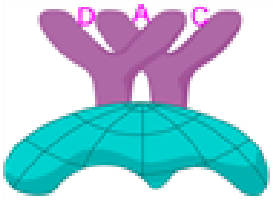

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Abstract

The United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) of European Union (EU), and the China Food and Drug Administration (CFDA) oversee and carry out the drug approval process. The goal of this project, sponsored by Hangzhou DAC Biotech, was to conduct a comprehensive comparative analysis of the drug approval process, with a focus on antibody drug conjugates (ADC). The results of this project show that the FDA has the fastest approval process, the EMA has the safest approval process, and the CFDA has the least expensive approval process. This report concludes with an evaluation of each of the three agencies approval processes and recommendations for small biotech and pharmaceutical companies seeking approval for newly developed drugs such as antibody drug conjugates.

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Executive Summary

Cancers present one of the greatest medical problems in today's world. According to the American Cancer Society, in 2012 alone more than 8.2 million patients died from cancer; that is approximately 22,000 cancer deaths each day (Anderson, 2015). Not only does cancer claim many lives, it causes much suffering for people who must undergo various treatments including surgery, chemotherapy, and radiation. However, with recent developments, antibody drug conjugates are now more than ever being pushed for cancer treatments. Pharmaceutical and biotech companies developing antibody drug conjugates (ADCs) seek to alleviate some of this pain and suffering by providing a far less invasive treatment. Antibody drug conjugates consist of a monoclonal antibody which has been chemically linked to a chemotherapeutic drug. The antibody is engineered to target certain, surface proteins which are expressed only by the malignant cells. As a result, only cancerous cells are eliminated and the surrounding healthy tissues are left completely intact.

Pharmaceutical manufacturers aim to market and sell their drugs across the globe. This process involves choosing an introductory market and designing testing and trials to minimize work repetition when entering markets in other regions. Given the massive amount of written policies and regulations, understanding a country or region's drug regulations and approval processes presents a significant challenge.

Project Goal

The goal of our project was to perform a comparative analysis of the United States Food and Drug Administration's, the China Food and Drug Administration's, and the European Medicine Agency's drug approval processes and to propose the most beneficial agency for Hangzhou DAC Biotech to seek their initial, ADC approval with. Our broad objectives were to research the three regions' drug administration processes (both the administrative authorization

and clinical trial procedures) and compare the time, cost, and required safety regulation components through literature reviews, case studies, and interviews.

Research Methods

To analyze these processes and develop a recommendation our team studied each region's centralized drug approval agency: the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the China Food and Drug Administration (CFDA). We conducted extensive literature reviews of these organization's official websites; written policies; relevant legislation; and peer-reviewed, medical-legal journals to collect the information needed to characterize, compare, and analyze the three organizations as well as their policies and procedures. We also examined case studies of both successful and failed monoclonal antibodies and drew important points and lessons from these previous examples.

Findings

We discovered that no single agency provides "the best" approval process. What is best for one company may not be best for another. The various factors of the approval process influence each other and make choosing an approval agency a complex decision. However, each agency provides a unique advantage. We found that the U.S. FDA provides the quickest approval process possible making it the best choice for companies racing for approval. We determined that the EMA requires the most precautionary procedures and is, therefore, the safest. Companies with adequate amounts of both time and money may want to consider seeking approval with the EMA. And we found the CFDA to provide the least expensive approval process, which also including clinical trials. The CFDA presents an approval pathway that may be most beneficial to companies looking for a more economically conservative approval process.

Recommendations

From our analysis of the FDA, EMA, and CFDA approval processes, we recommend that for further development of this project, collaboration with leading drug approval agencies around the world to develop a unified approval and submission process for drugs. This would allow research companies to have the option to view the materials and standards required for submitting their drug. This method would also allow the company more opportunities for submissions worldwide with only one set of submission materials. Overall, this would make a unified drug approval document submission pipeline and drastically reduce the overhead associated with developing multiple sets and formats of submission documents.

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Chapter 1: Introduction

Drug policies and regulations differ between the United States, the European Union, and China. A particular subset of oncology drugs, called an antibody drug conjugates (ADCs), has been a hot topic in the pharmaceutical industry in recent years and may see expedited government approval in the near future. Our project seeks to highlight the differences and similarities in the drug approval processes of the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the China Food and Drug Administration (CFDA). Companies looking to market an ADC drug for consumer use can refer to our project for a comparative analysis of these three regions' policies and approval processes. The information contained in this report may help companies choose the most appropriate agency for approval.

Understanding a country's drug policies and regulations can be a difficult task due to the sheer amount of legislation and the legal and medical terminology used. The language barrier also presents a formidable obstacle. Our team aimed to thoroughly research and understand the drug regulation (esp. ADC regulations) procedures of the United States, European Union, and China and determine which provides the most appropriate approval process for a company seeking approval for an ADC. In this report, we focus on three key points: the cost of approval, the length of the approval process, and the level of required safety precautions.

Previous work has been done on drug regulations comparing the US and Europe (Kashyap et al., 2015). We reviewed and made necessary updates to the scholarly articles as was required. We also included China's government regulations for their new and uprising ADC's into our evaluation. The peer-reviewed articles gave us a table of criteria by which to compare the three government agencies.

The goal of this project aims to provide a reader-friendly, summarized comparison of the federal drug regulations of the US, China, and the European Union specifically relating to the approval of antibody drug conjugates. Currently, there are consulting companies that help migrate pharmaceutical drugs from one country to another, but technical companies like Hangzhou DAC Biotech do not have access to a concise summary of these region's policies and regulations. Articles comparing the drug approval processes, like Kashyap and Raghunandan's article written in 2013, "Comparison of Drug Approval Process in United States & Europe", will serve a foundational role in our project. We will build off of their work to create an updated comparison and analysis specifically regarding antibody drug conjugates and includes China's drug approval processes as well. This project will provide Hangzhou DAC Biotech with a simple, side-by-side comparison of the three regions' approval processes and allow the company to efficiently understand the regions' regulations without reading through the massive amounts of legislation. Our comprehensive summary will give Hangzhou DAC Biotech an idea of the relative difficulties in gaining approval for a therapeutic antibody in the US, the EU, and China.

Chapter 2: Background and Literature Review

Cancers of various natures constitute one of the leading causes of death worldwide. According to the World Health Organization, in 2012 alone 14 million new patients were diagnosed with various cancers while approximately 8.2 million patients passed away due to cancer-related means (World Health Organization, 2015). Worldwide, pharmaceutical companies, patients, and governments, are pushing harder than ever for the development of new and innovative cancer treatments. Pharmaceutical and biotech companies continuously work to develop new cancer-fighting drugs, but still must undergo daunting approval processes prior to obtaining marketing authorization. The public's increasing demand for new oncology drugs is forcing drug regulatory agencies to develop accelerated approval processes in order to get these upcoming treatments in the hands of physicians for use on patients (Donnelly, 2014). Countries with developing regulatory industries such as China, India, and Brazil are still scrambling to adopt policies and processes to govern the drug market. At the same time, the United States and the European Union are adjusting their existing processes to accommodate the need for more streamlined, oncology drug approval practices including the use of antibody drug conjugates. In this chapter, we will define terminology frequently used throughout this report and describe the overall context and background of the drug approval process. This literature review depicts the importance of time, cost, and safety for all food and drug administrations to be successfully approved.

2.1. What are Antibody Drug Conjugates and Why Do We Need Them?

Physicians often treat cancer using traditional, and often times invasive, procedures such as chemotherapy, radiation, and surgery that can cause damage to healthy, surrounding tissue (Lightbulb Press, 2008). To eliminate the undesired potency of these conventional treatments a

new treatment, Antibody Drug Conjugates (ADCs), attempt to reduce the effects of chemotherapy on healthy cells. By combining the unique targeting abilities of monoclonal antibodies with the cancer killing ability of cytotoxic drugs, there is a greater level of control that significantly improves the delivery to targeted tissue (Peters & Brown, 2015). As a result, in contrast to chemotherapeutic treatments, ADCs minimize the exposure of healthy tissue and are, as a result, less severely affected.

Antibodies play an important role in the body's natural disease-fighting process. After production by the immune system, they flow through the bloodstream to seek out and tag receptors or antigens expressed on the surfaces of diseased cells. When attached, the immune system will then eliminate the tagged cell (Mandal, 2015).

Therapeutic antibodies can be customized to target specific cells. The unique functional mechanism of therapeutic antibodies allows them to be integrated into a standard cancer treatment consisting of chemotherapy or radiation. A huge part of developing antibodies is the ability to modify the part of the antibody which searches and tags infected cells. The modified part creates a hybrid that can be catered to tag a certain disease.

Monoclonal are antibodies produced artificially by a single clone cell or an identical cell line used as a binding agent (Genetech Inc, 2015) designed to bind to the surface of specific cells. They are advantageous due to the ability to produce unlimited homogeneous and monospecific quantities, making them effective tools for the development of therapies and diagnostics. Often, biologist engineers use these antibodies to bind to the growth factor receptors of cancerous cells (Chames, 2009).

Antibody drug conjugates are monoclonal antibodies (mAbs) that are attached to a biologically active drug by chemical linkers to form bonds. They have a unique targeting system

that is combined with a cancer-killing ability of cytotoxic drugs, which contain chemicals that kill cells. Together they allow the ADCs to be able to discriminate between healthy and diseased tissue. This advancement permits a greater control of the active drug by improving the accuracy of the delivery to the target tissue such as tumors and limit cancerous exposure (Werner, 2014). Currently, only two ADCs have been approved for cancer and are being used today. Many are in the clinical trials phase, however, many developers are also looking into the expansion of ADCs beyond oncology and have the potential to be developed to target any pathogen.

Early Developments

Early ADC testing, generation 1, was based on approved chemicals because the properties were known, however when used in clinical trials they lacked potency and low clinical activities. According to Stephen C. Alley's article "Antibody-Drug Conjugates: targeted drug delivery for cancer" it was found that "substantially more potent drugs that were too toxic to use in an untargeted manner have been more promising as ADCs". Generation 2 ADC testing was found to be more successful when using more stable linkers and stronger cytotoxins. ADCs represent a promising therapeutic solution for the clinical management of cancer. Today there have been three approved ADCs, two are still on the market and more than thirty ADCs worldwide are being evaluated in early- or late-stage clinical trials. The approval process for ADCs is a time and cost heavy procedure. Safety is the main concern for the drug approval industries while time and cost are the main concerns for companies trying to submit their ADC to place on the market.

In order to understand the background of this topic, we reviewed the literature from the official databases of the United States FDA, the European EMA, and the Chinese CFDA. The following sections explain the safety requirements and regulations for the preclinical, clinical and authorization phases and time differences of the overall drug approval processes.

2.2. Safety Requirements for Pre-Clinical Trials

During the drug development and research phase, all companies are held to a standard to ensure consistent, safe, quality work, resulting in the consensus of the drug regulating agencies that the data received was gathered in a reliable way. Our sponsor, at Hangzhou DAC Biotech, was especially interested in the rules and regulations specified in the current good laboratory practices and current good manufacturing practices entering into the clinical trials phase which, are the baseline requirements for any research laboratory or company. If not upheld, a company's credibility and marketing profits will greatly suffer.

Laboratory Notebook Requirements

Laboratory notebooks are an important part of research, they help record and organize data retrieved in experiments or for research. The title, date, materials used, objectives, procedure, methods, raw data, observations, results, and conclusions, can be found for the requirements of all major agencies (Food and Drug Administration, 2014). Additional written interpretations and technical records of instruments used are sometimes required for detail and precision in different agencies. It is recommended that the laboratory notebook is backed up electronically, but the final submission must be handwritten. Last and most importantly, the cGLP has requirements on how corrections are properly made. All three agencies require the use a single line to cross out the mistake combined with initials and the date of the correction.

Good Laboratory Practices (GLPs)

Current Good Laboratory Practices (cGLPs) provide a common baseline for scientific, research studies. These protocols or standards ensure that laboratory results can be reproduced when needed in the future and attempt to improve the accuracy of the studies (Robinson, 2003).

GLP protocols vary by region but today the Organization for Economic Co-operation and Development (OECD) provides a set of GLP protocols followed by thirty-four countries including the United States and the West-European countries (Organization for Economic Co-operation and Development, 2015). The UK's Medical and Healthcare Products Regulatory Agency, a member of the OECD, provides an internationally accepted definition of the GLP standard:

Good Laboratory Practice (GLP) embodies a set of principles that provide a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals (only preclinical studies), agrochemicals, cosmetics, food additives, feed additives and contaminants, novel foods, biocides, detergents etc.... GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can, therefore, be relied upon when making risk/safety assessments (Medicines and Healthcare Products Regulatory Agency, 2014).

The basic operating components outlined include test facility organization and personnel; quality assurance; facilities; apparatus, materials, and reagents; test systems; test references; items; standard operating procedures; performance of studies; reporting of study results; storage and retention of records and materials. Prior to analyzing the protocols, it is critical to define terminology. Clarification of terminology ensures a mutual understanding of the topic. Please see Appendix B for a complete list terms as defined by the OECP.

For a successful study, a *study director* (as defined in Appendix B) should take the lead role. This individual holds the ultimate responsibility for the study. He must establish or accept a proposed study plan and delegate high-level roles to qualified team members; the study director

may also amend the study plan as needed. They study director should quickly and clearly communicate the study's goals and objectives to quality assurance delegates and study personnel and provide all relevant participants with a copy of the study plan. The study director should also make certain that all important information is properly archived. Finally, the study director must sign off the completed study (The Application of the Principles of GLP to in vitro Studies, 1997). Both *in vitro* and histopathological studies play an important role in the pre-clinical trial application process.

In vitro data collection is typically favored over *in vivo* data collection where possible in an attempt to reduce the number of organisms subjected to biological testing. *In vitro* testing is considered particularly favorable during genotoxicity studies in which significant data can be collected without the use of multicellular organisms. Although *in vitro* data is particularly desirable the OECD notes that the GLP principles apply to all manners of *in vitro* studies unless an exception is granted. For these reasons, the OECD extensively documents the GLP procedures related to *in vitro* studies. To begin it is important to understand exactly what is meant by an "in vitro" study. The OECP defines this term as, "…studies which do not use multicellular whole organisms, but rather microorganisms or material isolated from whole organisms, or simulations thereof as test systems" (OECD Principles on Good Laboratory Practice, 1997).

For a study to provide a maximum of quality results, GLP practices must be followed strictly. Therefore, study personnel may require specific training in areas such as aseptic procedures and biohazard safety training. If a study neglects these training certifications, contamination could seriously affect a study's outcome. Additionally, management should provide all necessary resources to encourage the best possible study outcomes. When dealing with *in vitro* testing the study director should be particularly careful to adequately document the characteristics

of the test system and show that the test system performs adequately when compared to a reference system; this includes an analysis of positive, negative, untreated, and possibly control groups. Although the characterization regulations may seem confusing or tedious at first, these measures are in place to protect the quality of the study's results. This will often prove more difficult than when characterizing an *in vivo* test system. Test system characterization may warrant special case exemption in cases involving proprietary materials or test kits provided by a quality-audited supplier. Essentially, the entire characterization process simply serves to preserve the study's integrity (The Application of the Principles of GLP to in vitro Studies, 1997).

Good Manufacturing Practices (cGMPs)

Current good laboratory practices are listed in the Code of Federal Regulations Part 210 and 211. Part 210 is a clarification of definitions and Part 211 is the list of rules and guidelines that should be met. There are multiple difference between cGMP and cGLP, cGMP spans past the laboratory and will have rules on warehouse condition and production. From the FDA website, cGMP regulations contain "the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product". The "current" prefix of the cGMP refers to the rules that are consistently changing (The FDA also documents the rules that are not yet in place, but are under consideration). The cGMP specifies the minimum requirement needed for an inspector to pass a drug manufacturer. If a manufacturer does not meet the minimum requirement, the drugs it produces is labeled as "adulterated." Being labeled as adulterated does not prohibit you from selling the drug nor does it mean anything is wrong with the drug, but it does send a warning to consumers and the FDA. If upon closer investigation, the drug does, in fact, have unstable quality or the risks are greater than the known benefits, the FDA will ask the manufacturer to take the drug off the market. If the manufacturer refuses to do so, then legal action will be taken.

Drug production quality for most all agencies can be split into two parts. The definitions from the EMA government website are as follows: Good manufacturing practice "ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use." Good distribution practice (GDP) "ensures that the level of quality determined by GMP is maintained through the distribution network." That way, retail pharmacists can sell the medicine to the general public without any additional alterations to the drugs' properties. The GDP are stated in two directives, but only one pertains to investigational medicines for human use: Directive 2003/94/EC. While failure to meet cGMP in the US does not automatically disqualify your drug from selling, in the EU, failure to meet GMP does disqualify you from selling your drug.

2.3. The Pre-Clinical Trial Process

The Pre- clinical trial process is an essential part for the development of pharmaceuticals. A drug will not be approved for the market unless it is deemed safe by the country's agency responsible for the regulation of drugs. Successful and reliable research under both cGLP and cGMP must be completed and reviewed by the country's drug approval and regulation agency before the start of clinical trials. Drug companies are responsible for following the guidelines of each drug approval regulation agency when testing a drug. These policies are designed to maintain a high level of safety and regulation for the manufacturers of the drugs with the safety of future consumers in mind.

Submission Documentation Required

For an Investigational New Drug Application, several documents are required to ensure the safety of potential patients. Information including the contents of the drug and its biological properties, chemicals and compounds needed to produce the drug, any conceivable variation of the drug, an overview of the manufacturing process for the drug is needed, and the levels of the agents

within the drug to classify it (Lumpkin, M., 1995). The purpose is not only for approval but also for documentation if there is an accident within clinical trials or after the drug is released, the documentation can be used to determine what part of the drug caused a problem. The drug can then be adjusted accordingly.

2.4. The Clinical and Post-Clinical Trial Processes

As shown below in Figure 1, clinical trials put the company's work to the test involving many patients. They strive to achieve success through clinical trials in the shortest amount of time with the least amount of money spent to get it there. If a company fails a phase in clinical trials or they didn't comply with the cGMP or the cGLP they have a chance to revise and redo the trials. Redoing trials, however, take a lot of time and even more money.

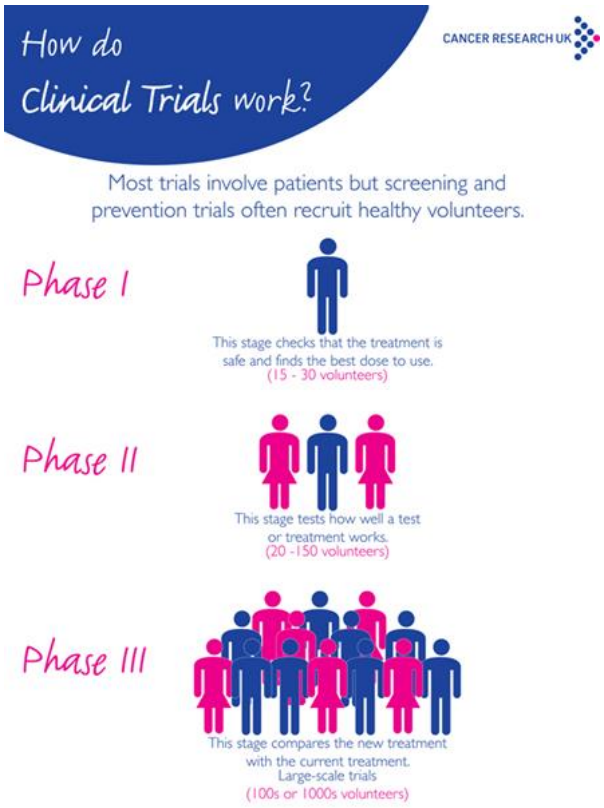

Figure 1: Pre-market phases of clinical trials (Arney, 2012)

Additionally, the EMA, FDA, and the CFDA have their own laws and regulations to maintain the safety and integrity of the process that extend the time spent conducting clinical trials even further. In this stage, it is important that the company's work in the preclinical trial process was completed correctly and in a coherent format so that any problems can be fixed immediately.

Time Comparison for Clinical Trials

During the Clinical trial process, different food and drug agencies around the world require a comparison study between either one or two with the addition of a placebo to evaluate the differences and similarities about the drug in question. These regulation differences sometimes cause agencies reviewing the same drug to have diverse decisions for the approval of the drug (Olson, 2014). The process can take a longer amount of time for one agency and can result in a slower approval for market validation. However, with additional drug comparisons and testing precautions, even if the approval process is slower, the drug being reviewed can be deemed unsafe earlier in the approval process saving time and money.

2.5. The Authorization Process

The last step of the process is the authorization process, where a drug is submitted for review to its respective governing agency. The agency will review the drug and the corresponding material that was submitted and make a decision on the authorization of the drug. This process, in most cases, takes over a year to complete and requires the submission of supplementary data from the company. Most companies at the authorization stage are able to apply for an accelerated approval process resulting in several months shorter waiting time for the approval of their ADC submission.

Accelerated Programs

Both the FDA and EMA have ways to accelerate the drug approval process. The FDA can give up to four approaches (based on the current state of the market, and how convincing the data provided is) to speed up the approval process. The EMA has two approaches to accelerating approval. Depending on the approval process, the renewal license would be sooner than 5 years to validate sooner. One of the four ways the FDA can expedite a drug to the market is through accelerated approval. This is the most important and fastest way to get the drug on the market because it encompasses the other three. All previously approved ADCs by the FDA went through this accelerated approval process (Donnelly, 2014). The approval process allows the ADCs to enter the market quicker than if it was a non-priority review allowing clinics to have access to them as soon as possible.

2.6. Our Project

As a significant company in the field of therapeutic antibody developments in China, Hangzhou DAC Biotech was keen to learn about the approval processes as they relate to monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs). They wanted to learn about the overall approval process and specifically the process for entering into the clinical trials phase. Our team compared and analyzed the drug approval process of the United States, Europe, and China to suggest the best market for Hangzhou DAC Biotech and any new and uprising drug company to introduce their ADC into. An ideal market can minimize the time and monetary investments while maximizing safety precautions. There are many regulations and requirements needed to approve an ADC. Through our research and analysis, we have provided a concise comparative study for small research agencies looking to approve a drug in any of the three major food and drug agencies mentioned. To understand more about the drug approval processes, it was

important to analyze research article, medical journals, and textbooks, conduct interviews and collect research data on FDA, EMA, and CFDA approval process documentation. The next chapter discusses our methods for how we gathered data to accomplish our goals.

Chapter 3: Methodology

The purpose of our project was to compare the drug approval processes in the United States, the European Union, and China. The major stakeholder in this project, Hangzhou DAC Biotech, is interested the approval processes specifically relating to monoclonal antibodies (mAbs) and antibody drug conjugates (ADCs). Hangzhou DAC Biotech hopes to begin clinical trials with their antibody drug conjugate in the next year so they are particularly interested in a comparative evaluation of the three stated regions approval processes. Our goal was to assess each region's agency with respect to the degree of mandatory safety precautions, the time required by the agency to review the new drug application, and the new drug application fee specifically as they relate to ADCs and mAbs. In this project, our goal was to propose a market for Hangzhou DAC Biotech to introduce their ADC into–a market which minimizes the required amounts of time and money but maximizes safety precautions. Our team developed a set of objectives to complete as we moved towards our goal. In this chapter, we discuss our goal and objectives and what methods we chose to gather data to accomplish each objective. This chapter is organized to address what methods we used to evaluate the overall process, the safety requirements, and animal testing regulations of each agency, and additionally, what we can learn from case studies of failed approval of drugs.

Objective 1: What Does Each Agency's Overall Process Look Like?

To achieve our first objective, it was important to understand the background of each organization and understand each region's general, drug-approval process. The reason is that we need to understand the ADC approval process, familiarize ourselves with the highly specific and technical terminology of the field, and begin identifying drug approval officials and experts. To complete this objective we conducted a literature review of a variety of secondary sources including various articles from each agency's official website, presentations given by agency

officials, and peer-reviewed, journal articles and books written by experts from academia and industry. The secondary sources we selected provide a reliable method of research because the authors work for the same accredited agency responsible for federal drug regulation. The sources we chose to review from academic journals have been peer-reviewed and can be depended upon for accuracy. We chose to conduct a literature review due to the availability of information on each agency's official website as well as independent evaluations conducted by other experts.

To obtain information regarding the United States' chemical and biological drug approval processes we consulted the FDA's official website found at www.fda.gov, for information regarding the European Medicine Agency's chemical and biological drug approval processes we visited their official website which can be found at www.ema.europa.eu, and for information about China's Food and Drug Administration's chemical and biological drug approval processes we visited their website found at eng.cfda.gov.cn. We also collected data from official agency sources such as presentations and lectures given by officials from the agencies as well as drug regulation professionals from various pharmaceutical companies. We studied "Regulatory Considerations of Antibody Drug Conjugates" written by Sarah Pope Miksinski, the Acting Division Director for the Division of New Drug Quality Assessment 2 for the FDA's Office of New Drug Quality Assessment, and Marjorie Shapiro from the FDA's Division of Monoclonal Antibodies. We consulted a presentation titled "How to Get a Drug Approved by the FDA" given by the FDA's Director of the Division of Drug Oncology Products, Robert Justice. Additionally, we collected data from the China Food and Drug Administration's website we carefully reviewed a presentation called "Introduction to the CTA and NDA Process in China" given by Jie Zhang of Abbot's China Regulatory Affairs Division and Peter van Amsterdam an expert in clinical pharmacology and bioanalytics for Abbot in the Netherlands.

Translations

A significant issue encountered while conducting the literature reviews previously discussed was the lack of information about and presented by the CFDA. The agency was only formed recently and the major language of China is Mandarin. Having limited information because of the age of the agency and access to the information because they were presented in Mandarin contributed to the limitation of our study. However, online translation tools such as Google Translate were used to help translate some of the information to English. For the analysis of the cost of clinical trials, our group consulted students from Hangzhou Dianzi University to help us translate the documents. This allowed us to compare the costs of the CFDA to the other agencies.

Interviews

In order to discuss ideas with experts and hopefully generate some new thoughts, our team decided to contact experts including various agency officials and experts from academia and industry. We carefully selected authors whose work we had read and emailed each expert a brief, semi-structured interview specifically tailored for the interviewee based on their article referenced in Appendix A. We chose this open-ended format so that we could guide the discussion yet allow the experts to introduce new ideas. From these interviews, we hoped to gain opinions on the relevant differences between the three regulatory agencies and possibly some new ideas on our comparison of the processes. Unfortunately, our team did not hear back from our contacts with the exception of one.

One contact, Dr. David Taylor from King's College London replied we settled upon a different approach to gathering our data. We proceeded to confirm our findings with this one expert. Response from an expert would help us gain insight into a professional’s views of the relative speeds and safety precautions taken by the FDA, CFDA, and EMA. To accomplish this

we wrote a brief explanation of our rankings of agencies in respect to time, cost, and safety and asked our contact to simply comment on whether or not he agreed with our conclusions that the FDA provided the quickest means of approval, the EMA required the most safety precautions, and the CFDA provides the least expensive approval process. Despite numerous attempts to contact him via email and due to limited time, we were not able to interview Dr. Taylor.

The methods we employed were reasonable due to the highly specific nature of our questions. The information we required is not common knowledge and would only be possessed by experts in the drug approval field so we were strictly limited in terms of suitable data gathering methods.

Objective 2: How Do Each Agency's Good Laboratory Practices Compare?

Next, it was important to examine the stated Good Laboratory Practices (GLPs) of each agency. GLPs constitute a significant part of an agency's safety precautions and we sought this information to better inform our safety analysis of each agency. We chose to answer this question by completing a literature review of each agency's GLP requirements. We examined two sources: the Organization for Economic Co-operation and Development (OECD) and the China Food and Drug Administration. Both the United States and the European Union participate in the OECD and follow the OECD's official Good Laboratory Practices. We discovered all necessary information on the OECD's GLPs in a series of sixteen documents made available on the OECD's website specifically devoted to the defining and establishing good laboratory practices. Since China does not participate in the Organization of Economic Co-operation and Development and the OECD protocols do not apply to China, we searched the China Food and Drug Administration's website to identify their Good Laboratory Practices. One limitation we encountered in meeting this objective was that the CFDA provides information on how to get a facility certified in good

laboratory practices and states some basic practices but does not clearly state details as to what those practices are as the OECD does. We then turned to the World Health Organization's (WHO) which has hosted a number of GLP workshops for officials of the CFDA. We searched the WHO's online database for information but the WHO did not provide any additional information on the CFDA's GLPs either. Due to our limited time in our project, we were unable to contact the directly contact the CFDA and obtain information on China's pharmaceutical GLPs. This information is needed to provide a complete picture of the CFDA's GLPs in order for a proper comparison with those of the United States and the European Union.

Objective 3: How Do Each Agency's Good Manufacturing Practices Compare?

Along with each agency's GLPs, we decided to conduct a literature review of each agency's good manufacturing practices documents (GMPs). Information about each agency's GMP requirements would be factored into our agency safety-analysis. Initially, we searched for information on the agency websites; these searches uncovered a large amount of related information. To complement the information we collected from agency websites, we looked for academic articles which highlighted the differences in manufacturing practices and found a number of those as well. We chose to conduct a review of information on agency websites due to its availability and authority and we chose to search for academic articles as a means to introduce aspects of other's analyses that we could integrate into our own.

Objective 4: How Do Each Agency's Laboratory Notebook Requirements Compare?

Laboratory notebook requirements play an important role in the recording of experimental data and it contributes significantly to the safety of a process. The integrity of laboratory notebooks can directly affect the subsequent interpretation of the experimental data. That interpretation then

determines what happens next–whether the drug continues to clinical trials or not. Agencies with strict notebook requirement encourage better data interpretation and as a result possibly reduced risks for clinical participants. Therefore, laboratory notebook requirements are important and we wanted this information to factor into our safety evaluation. We sought to perform a literature review of articles on agency laboratory notebook policies from agency websites as well as the ScienceDirect and MedLine databases. These sources did not contain the information we sought so we searched for scientific, consulting companies. We discovered a German technical communication consulting company called FITT through our literature research. It is a daughter company of MFG Baden-Württemberg, established in 1995. Consulting organizations must provide reliable information in order to continue the business, and MFG Baden-Württemberg has been in business for approximately twenty years at the date this paper is written so we believed it to be a reliable source of information. We downloaded and studied a presentation made available online by FITT which contained the information needed to complete our laboratory notebook objective.

Objective 5: What Can Be Learned from Case Studies?

Case studies are an excellent means of learning. What better way to learn than from the experiences of others? Researchers can learn to avoid mistakes and pitfalls without having to experience them and can receive guidance on the best direction to take. We examined case studies written by U.S. FDA officials to gain insight into where drug sponsors went wrong in the approval process and possibly how the agencies deal with violations of protocol or poor experimental techniques. We utilized the ScienceDirect database to obtain an article called "The Birth Pangs of Monoclonal Antibody Therapeutics: The Failure and Legacy of Centoxin" written by Lara Marks a renowned professor in the Department of Primary Care and Public Health from King's College

London. We carefully read Marks' narrative of Centocor's attempted approval of Centoxin, a monoclonal antibody. Then we studied her analysis of why the drug was rejected, where the company had gone wrong, and what lessons could be applied to sponsors applying for mAb or ADC approval in the future. We used information learned from the case study of Centoxin to inform our evaluation of the FDA's safety measures.

Objective 6: How Do Each Agency's Animal Testing Requirements Compare?

Animal testing is an integral component of the drug approval process. The amount of animal testing required dictates how much money and time must be spent on collecting data before the drug can be tested in humans. Therefore, we decided to investigate the animal testing requirements of the three agencies and try to gain quantitative results. For the FDA, according to the article, "Product Development Under the Animal Rule," the FDA only provides guidelines for animal testing. This made it difficult to obtain quantitative results. Since the FDA guidelines provided no quantitative information, we decided to research past drugs to see the animals they used for the different types of toxicity testing. We examined a previous study published in the article, "U.S. Food and Drug Administration", published by the People for the Ethical Treatment of Animals (PETA) which referenced an FDA presentation and provided quantitative animal testing data for the average drug. This allowed us to provide our sponsor with a rough estimate about the number of animals they would need to conduct testing on. We found that the drug manufacturer is responsible for designing the animal test and giving conclusive evidence to the FDA about why they used the animals they did and what type of toxicity each test was for.

Chapter Summary

Throughout our project, the primary limitation we encountered was the lack of method diversity. This lack in the variety of methods results from the specific nature of our research which dealt with cutting-edge biotechnology studied by a fairly small group of researchers. As a result, there were only three practical means of getting this data from the experts, reviewing publications written by this small group of experts, performing case studies of similar drugs, and conducting interviews with these same experts. Also, the limited time we had to complete the project made it challenging to gather data from an interview as the experts are difficult to contact. The relevant information and findings about each agency's ADC approval process that we uncovered while employing the described methods is discussed in the following chapter.

Chapter 4: Findings and Recommendations

Through the analysis of information gathered from FDA, EMA, and CFDA databases, research article, medical journals, and textbooks, we developed the following four findings regarding the safety, time, cost, and future perspectives of the overall approval process of an antibody drug conjugate.

Finding 1: The European Medicines Agency has the Strictest Policies

Food and drug administrations around the world vary in their approval processes with ADCs, especially with time, cost, and safety. Our research focused on these variables because they are significant to companies trying to approve their ADC successfully in the shortest amount of time with the least amount of cost. The EMA prioritizes the safety of future patients with the most regulated policies to approve an ADC out of the three agencies. In addition to the good laboratory principles and good manufacturing practices guidelines, specific laws and regulations from the official EMA database, specific to ADCs are explained in this section.

Good Laboratory Practices

To determine the strictness of laboratory regulations that affect the quality of laboratory data that directly relates to the safety of the drug, we conducted a literature review that determined that the European Medicines Agency has the strictest standards in terms of antibody drug conjugate approval policies. Both the United States and the countries of the European Union are members of the Organization for Economic Co-operation and Development (OECD) follow the good laboratory principles (GLPs) provided by the OECD (Organization for Economic Co-operation and Development, 2015). China, however, does not participate in an international, standardized, protocol system but provides pharmaceutical companies with their accepted GLPs through the CFDA. Companies seeking approval in China should apply for GLP certification from the CFDA

(Good Laboratory Practice (GLP) Certification, 2013). This certification states that the facility is in compliance with GLP requirements. The OECD GLPs contain specific project role designations and establish a structured hierarchy which provides means of accountability and creates clear lines of communication—both of which are critical to the integrity of a study. The CFDA does not provide such clear definitions of roles and enforces significantly fewer regulations than does the FDA and EMA. Additionally, the OECD members place a high emphasis on quality control and the OECD GLPs provide specifics about who is to carry out quality control audits as well as the basics of how to carry out such inspections. The CFDA's GLP protocols do require quality control standards but seem to take on a lighter role than they do in OECD member countries.

Good Manufacturing Practices

Good manufacturing practices (GMPs) comprise a related means of our safety analysis. They ensure precision in drug manufacturing and consistency between product characteristics and marketed characteristics such as strength and purity. It is of the utmost importance that companies manufacture their product in a controlled manner both for clinical trials as well as when the drug reaches the market. To ensure this, drug regulatory agencies provide drug sponsors with GMPs which must be followed during the manufacturing process. The varying levels of manufacturing regulation affect confidence in the product's quality. Once again we performed a literature review of each agency's available GMP information and in doing so we found that the EMA regulates manufacturing the most, followed by the U.S. FDA and then the CFDA. All three agencies regulate the critical aspects of manufacturing, but the EMA provides a more specific level of regulation. The U.S. FDA and the CFDA leave many items to be defined by the manufacturer while the EMA lays out in detail the requirements leaving little room for the manufacturer's interpretation. For example, the FDA then uses the word "appropriate" as a descriptor; this leaves it up to the

manufacturer to deem what is “appropriate” (Title 21 Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals, 2015).

The FDA does require audits to ensure that the manufacturers do interpret the regulations in a meaningful manner which protects employees and consumers, but it still allows manufacturers a higher degree of freedom than is allowed by the EMA. As for the CFDA's GMPs, they are a bit less restrictive than even those of the FDA. In many respects, they closely resemble the FDA's, but they provide fewer details and directions in certain areas (Good Manufacturing Practices for Drugs, 2010). The CFDA’s official database contains an article titled “Good Manufacturing Practice for Drugs” which provides the formal GMPs of the CFDA. The article frequently uses terms such as “appropriate” and “sufficient” in the same manner as the U.S. FDA which leaves interpretation open to manufacturers. As is the case with GLPs, the CFDA requires manufacturers to obtain a certificate stating that their facility and procedures satisfy relevant requirements and that the facility has permission to manufacture their product.

Specific European Medicines Agency Regulations

During clinical trials the EMA requires the ADC to be involved in a “three-arm study”, wherein the drug in question is compared to a comparator drug and a placebo, unlike the FDA which compares the drug in question to only a placebo (Olson, 2014). When entering clinical trials the EMA has strict regulations to inform their patients of any modified organisms such as ADC, which they will be coming into contact with. Under the regulation (EC) No 726/2004 of the European Parliament and the Council, medical products for human use require the EMA to account for several safety risks. A direct quote from Article 6 section 2 of the Offical Journal of European Union published in 2004 states:

> If there is a case of a medicinal product for human use containing or consisting of genetically modified organisms, the application shall be accompanied by: A copy of the competent authorities' written consent to the deliberate release into the environment, the complete technical informational record of the product, the environmental risk assessment, and the results of any investigations performed for the purposes of research or development.

The EMA sets these guidelines to help protect not only the patients directly involved but also the drug developers. With additional regulations, drug developers are able to submit their drug knowing that it is as safe as it can be and will know how to solve any problems the drug may have from their thorough research and analysis.

After clinical trials are completed the drug is submitted to their country's food and drug administration. One of three authorizations can be issued by the EMA to a drug sponsor: normal approval, conditional approval, or an exceptional circumstance approval. A normal approval licenses the company to market their drug for five years. Nine months prior to the license expiration the sponsor may submit an application to renew along with clinical data collected during those four years and three months. This data will determine how the EMA will renew the license. If the data shows a low risk and high benefit in clinical use, the EMA will issue a second license of unlimited validity (Donnelly, 2014). If the data remains inadequate to make a final decision, the EMA will issue a second, five-year license after which the final decision will be made, whereas the FDA will allow firms to market the drug indefinitely (Olson, 2014).

The EMA issues conditional approval permits to companies or sponsors of drugs who lack appropriate clinical data but claim significant health benefits linked with their drug. The approval, however, is dependent on two main points: the sponsor must provide evidence suggesting that the

drug's benefits outweigh the risks and the sponsor must agree to collect and provide clinical data continuously. In these cases EMA will award a one-year marketing authorization which can be renewed. Conditional approval is not meant to last long term so when an adequate amount of clinical data is collected and submitted the EMA will promote the sponsor or company to a normal approval license.

Finding 2: The United States Food and Drug Administration is Able to Approve Antibody Drug Conjugates in the Shortest Time

Through the data gathered from published documents retrieved from the agencies' websites, we determined that the FDA has the fastest review and approval programs. The time taken to approve an ADC varies significantly depending on the agency and their accelerated approval programs as shown in Table 1. The preclinical and clinical trial timelines are very similar between agencies, they vary mainly in safety regulations required to enter into clinical trials. The authorization process directly follows the clinical trial period.

Agency	Non-Priority Review Time	Accelerated Approval Time
FDA	10-12 months	6-8 months
EMA	14 months	12 months
CFDA	7-12 months	

Table 1: Normal and accelerated approval times for an antibody drug conjugate.

Table 1 shows the time needed for the approval agencies to review all the information submitted with the drug and the trial results. Several agencies have adopted policies that allow an expedited approval process to allow ADCs to be put on the market as soon as possible.

Time for Authorization Process

The time is similar to process a normal drug for the FDA and EMA. However unlike the FDA the EMA has seven different committees to evaluate the received medical applications. The committee pertaining to ADCs is the CHMP, Committee of Human Medicinal Products. The CHMP usually develops an opinion of the drug within 210 days. If the application is accelerated, the process is reduced to 150 days. After the CHMP makes an opinion, the European Committee determines market authorization. Clock stops are another unique element to the European process. Clock stops average 4 months for an application and are time periods in which the application responds to questions from the CHMP. The EMA approval process for a non-priority, not accelerated approval takes about 14 months, while the FDA takes on average 12 months to complete the authorization process, and although a Category 1 CFDA approval estimates a review period of 7-12 months (Optimizing Drug Registration in China: Category I Route, 2013), the lack of ADCs approved in China is a dissuading factor.

Accelerated Approval Programs

The FDA and EMA both have programs to accelerate the drug approval process. The FDA can give up to four while the EMA has two approaches to accelerating approval. Both the EMA and the FDA can classify drugs as an orphan designation, which is available to medicines who target a small population. It provides incentives to develop drugs in a small population market. In total the FDA can classify drugs as orphan designation, fast track, accelerated approval, breakthrough therapy, or priority review, the EMA can classify drugs as orphan designation, or accelerated assessment and the CFDA can classify drugs based on six categories. Category 1 drugs are drugs not yet approved in any country. Category 6 drugs are generic drugs with existing national standards in China (Optimizing Drug Registration in China: Category I Route, 2013).

One of the four ways the FDA can expedite a drug to the market is through accelerated approval. Incorporating the three other accelerated approval programs, accelerated approval is the most important and fastest way to get the drug on the market by the FDA.

On average the FDA accelerated approval program takes about eight months to approve an ADC from submission to active market planning. A non-priority review takes about twelve months. Planning meetings and filing decisions both take about 45 days. About 6 months after authorization is granted the new drug is distributed into the market for the accelerated FDA ADC program (Beishon, 2014). 6 months is only an average, however.

If the FDA could not grant an accelerated approval based on the surrogate endpoint, that is, a laboratory measurement, radiographic image, physical sign or another measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit, it may choose to grant another way to expedite the drug.

- **Fast Track:** Fast Track drugs are determined based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition if left untreated, will progress from a less severe condition to a more serious one. Being approved for Fast Track designation allows more frequent meetings with the FDA to discuss the drug's development plan and rolling review, which allows incremental submission of a Biologic License Application or New Drug Application to the FDA (as compared to filling out the entire application).
- **Priority Review:** Prior to approval, each drug marketed in the US must go through an FDA review process. In Priority Review, the FDA's goal is to take action on an application within 6 months as compared to 10 months under standard review. A drug is considered for priority review if it would be a significant improvement in the safety or effectiveness of a

treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

- **Breakthrough Therapy:** The FDA expedites the development and review of drugs that may demonstrate substantial improvement over available therapy. Substantial improvement refers to "an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease." A drug that receives Breakthrough Therapy is also eligible for all fast track designation feature, intensive guidance on an efficient drug development program, and organizational commitment involving senior managers. The FDA will review Breakthrough Therapy requests within 60 days of submission (Fact Sheet: Breakthrough Therapies).

The EMA provides two means for the accelerated approval of a drug. These two pathways are:

- **Conditional Approval:** The EMA may grant conditional approval authorization to a company or sponsor who lacks a standard amount of clinical data but presents a drug with preliminary data which suggests major health benefits or markedly improved patient conditions
- **Exceptional Circumstance Approval:** The exceptional circumstance approval is quite similar to conditional approval. The EMA may issue an exceptional circumstance marketing authorization to a company of sponsor who submits an inadequate amount of supporting data due to the rarity of the targeted condition, scientific/technological limitations, or ethical constraints.

Although it varies widely, the whole authorization process on average takes about fourteen months, two months longer than a non-priority review for the FDA. The delay in the approval process is a

combination of additional requested information and price negotiation. Unlike the EMA, the US has a set price and does not negotiate for the price on the approved drug (Beishon, 2014).

Finding 3: The China Food and Drug Administration is the Least Expensive Process

While conducting our literature review, despite the FDA, EMA, and CFDA databases explaining the required application and annual cost, some expenses were not explained or published in their overall expense portfolio. From our research using the official governing databases and regulatory guideline, we were able to deduce the total application cost and authorization cost of the three agencies, and list the additional charges relating to the type of drug and work environment it is developed in. For consistency we converted the different currency in terms of United States dollars as shown in Table 2.

Agency	Application Cost	Annual Costs
FDA	$2,374,200	$699,650
EMA	$300,059	$107,641
CFDA	$97,922	Dependent on providence

Table 2: Comparison of the application and annual costs for submission

The cost for a drug application is an important factor to manufacturers deciding where to market their drug. There are many types of fees for the three regulatory agencies. The US FDA has an application, establishment, and product fees. The EU EMA has a marketing authorization application fee, extension, variation, and annual fees. The CFDA does not have any major fees except for those that are required for their providence.

United States FDA

According to the Prescription Drug User Fee Rates for Fiscal Year 2016 published by the Federal Register, the US FDA Drug Application cost is $2,374,200. Half of this fee is a clinical trial report review while the other half is the authorization to market the drug. The annual cost the FDA asks for is $699,650. This cost is a combination of the establishment fee of $585,200 paid by the owners or operators of business planning to manufacture any drug, and product fee of $114,450 which is the cost to register the product as an approved drug. Fees for applications have been increasing from year to year. In the 2014 fiscal year, the New Drug Application fee with clinical data increased by 10.7% (Gilmore & DeBartolo, 2013). In some instances applications fees can be waived depending on the submitted drug, such as if it as the ability to protect the public health more so than a previously approved drug (Frequently Asked Questions on Prescription Drug User Fees, 2015).

European EMA

The EU EMA has flat application fees and annual renewal fees. After converting from the Euro to the US Dollar, the EMA fees are substantially cheaper. At this time, the conversion rate is 1 Euro = 1.08 US Dollar. According to the Explanatory note on fees payable to the European Medicines Agency by the EMA published on July 2015, one single marketing authorization application cost for human medicines is $300,059. If there are any needed modifications to the drug labeling such as active ingredients, available strengths, pharmaceutical forms, or the route of administration then a fee of $90,061 is charged. Another form of modification, known as a Type-II variation, is a major change in the drug that may affect the quality, safety, and efficient, and also has a fee of $90,061. Lastly, the EMA charges an annual maintenance fee of $107,641. (Fees payable to the European Medicines Agency, 2015) Fee reductions and incentives are available. As

a brief overview, there are exemptions noted in Section 5, Fee Exemptions of *Explanatory note on fees payable to the European Medicines Agency.* Of those that pertain to ADCs, Micro, small or medium-sized enterprises, orphan medicinal products, advanced therapy medicinal products, and Medicinal products for minor uses may be applicable to an ADC drug submission to waive fees.

Chinese CFDA

According to *CFDA Drug and Medical Devices Application Fees* an article published by the CFDA in 2015, the type of administrative fees are also annual and flat amount. The current exchange rate for 1 US dollar is 6.37 RMB. For domestic products, translated from Mandarin Chinese and converted from RMB to US Dollar, the total cost for market approval in china is $97,922. The application cost to register a new drug with clinical trials is $30,130. There is also a cost to produce and market the drug, which is $67,792 for the administration review. Supplements to an application or any additional changes to the drug after submission cost $15,630. The annual renewal rate varies depending on what province from china the applicant is located. There are also waivers available to small Chinese companies that may reduce the cost for market approval.

Mentioned above are the administrative fees incurred after submitting a Biologics License Application and New Drug Application to the FDA, a new market authorization application to the EMA, or a new drug application and marketing application to the CFDA. The majority of costs incurred from a drug in development to market is from the clinical trials, the most expensive of which are phase III clinical trials. In terms of short-run flat fee and the long-term annual fees, the CFDA is the cheapest. With relation to our sponsor, the CFDA offers waivers to small businesses which provide incentive to the CFDA application process. As a price comparison with the FDA, the FDA's single application fee is 79 times more expensive than the CFDA market-authorization fee.

Finding 4: Three Approved ADCs, Two Remain on the Market Today

A case study is a process or record of research in which detailed consideration is given to the development of a situation over a period of time. We found case studies to be very useful in identifying the mistakes that were made in the developments of not only ADCs but for research laboratories in general. Following is a summarized case study, of a company called Centocor Biotech and the failed approval process of their monoclonal antibody, Centoxin. *The Birth Pangs of Monoclonal Antibody Therapeutics: The future Legacy of Centoxin* by Dr. Lara Marks a medical and biotechnological historian at King's College London provides terrific insight into the process of developing, testing, and approving a monoclonal antibody. Successful case studies of two ADCs still on the market today are later described in this section.

Case Study of Centocor's Centoxin

In 1986 Centocor, now known as Janssen Biotech, began development for HA-1A, a monoclonal antibody (mAb) they had recently developed to treat patients with Gram-negative sepsis later renamed the mAb Centoxin. In 1991, after the successful completion of all three phases of clinical trials, Centoxin received validation in Europe when Britain, Germany, France and the Netherlands issued their approval in response to the European Committee for Proprietary Medicinal Products' recommendation for the administration of Centoxin for the treatment of patients with Gram-negative sepsis. However is was soon after that, Centocor's troubles began when a U.S. federal court decided that Centocor's patent for Centoxin infringed upon Xoma's patent for its IgM competitor mAb. During the legal battle which ensued the United States National Institute of Health released the results of a study they had recently completed which examined the effectivity of toxin on a special breed of eagles. The study's results brought into question the beneficial effects of Centoxin. The study showed no statistically significant effect of the mAb on

Gram-negative sepsis and even raised concerns about the safety of patients receiving the treatment. In 1992, despite concerns over the drug's effectivity and safety, investors continued to expect Centoxin's approval and hospitals prepared administration protocols in anticipation of the complete approval.

A few months later Centocor received some concerning news from the FDA. The FDA had discovered that in a violation of good laboratory practices (GLPs) and standard operating procedures (SOPs) certain executives and statisticians had seen un-blinded, raw data which had produced a biased interpretation. As a result, the FDA demanded that Centocor produces a significant amount of new information and data–a demand the company knew would cost them much valuable time and money as they raced against Xoma to create an effective mAb. Stock value dropped by 19% once investors got the news.

Once the new, and now unbiased, data was submitted the FDA decided the data was insufficient to issue a complete approval. FDA officials noticed multiple inconsistencies in the trials. Researchers had set varying endpoints for patient observation and used multiple procedures to account for patients who failed to provide follow-up data. Once again they requested that Centocor begins another round of clinical trials to collect more patient data. Once, again stock value plunged and $1.5B of Centocor's market capitalization disappeared. Major investors began filing lawsuits again the company claiming that security laws had been violated; the Centoxin was on the brink of collapse.

In July of 1992, Centocor formed a cooperation with Eli Lilly gave Centocor an immediate $100M in return for a 5% stake in the company. After collecting the money, Centocor once again began phase three clinical trials. However, results proved disappointing and further testing come to a halt within six months; Centoxin was dead.

By examining this case, we found the importance of maintaining good laboratory practices (GLPs) as well as developing and adhering to a quality set of standard operating procedures (SOPs). Although the specific details remain unknown, it is clear that Centocor did not adequately uphold the GLPs and SOPs. The first time the FDA requested additional information because the wrong people had been allowed to see the data. This problem could have been avoided if Centocor had carefully observed the hierarchy laid out in GLPs. The second time the FDA requested a new round of clinical trials it was clearly due to poorly written and upheld standard operating procedures. The SOPs should have clearly defined the length of patient observations and the methods used to account for patients who did not provide follow-up data. Centocor either failed to define methods to deal with these important issues or failed to follow through with their SOPs. In the end the data was so badly mangled that statisticians could not accurately interpret the data and they abandoned the drug.

Case Study of Adcetris

One of the first ADCs approved that is still on the market today is Adcetris. It was developed by Seattle Genetics and Takeda Pharmaceutical. In the FDA, Adcetris was approved on August 19, 2011, with an Accelerated Approval designation. It's BLA was submitted February 28, 2011, which gives a 6-month range from when the clinical data and application were submitted, to the final approval date (Drugs.com, 2015). In the EMA, Adcetris, with an orphan designation, was granted conditional approval on July 19, 2012. The application was received by the EMA on May 31, 2011, which leaves a 14-month range from date of submission to date of approval (EMA Assessment report for Adcetris, 2012). In China, the only found use of Adcetris, medical name, Brentuximab vedotin, was administered to a patient in 2013 (Cao, 2013). According to the CFDA database, the CFDA provides no records of Adcetris, medical name Brentuximab Vedotin, in the

imported drug database nor in the database of approved Active Pharmaceutical Ingredients (APIs) and API manufacturers. The FDA approved the Adcetris application 8 months faster than the EMA.

Case Study of Kadcyla

The second ADC approved and still available on the market is Kadcyla, medical name ado-trastuzumab emtansine. Genentech, a subsidiary of Roche, holds the license globally. In the FDA, Kadcyla, through an accelerated approval process, was approved on February 22, 2013. It's BLA was submitted on August 26, 2012, which leaves a 6-month review process (Kadcyla, 2014). According to the EMA's documentation on Kadcyla, Kadcyla's EPAR application was submitted on August 30, 2012, and approved on September 19, 2013. It's review took 13 months to complete in the EMA. According to the CFDA, the import drug records do not contain records of Kadcyla but do contain records of Herceptin, medical name, trastuzumab. Herceptin is Kadcyla but without chemotherapeutic toxins. Due to this comparison focusing on antibody drug conjugates and Herceptin being a monoclonal antibody, Herceptin's CFDA data was not used. Genentech decided to apply to both the FDA and the EMA simultaneously. The FDA designated Kadcyla as an accelerated approval while the EMA did not. The FDA completed the review process 7 months earlier than the EMA.

Chapter Summary

Based on the information explained in this section, we determined three major findings for the approval process of ADCs. First, the European Medicines Agency takes the most precautionary measures to ensure the safety of approved drugs. Second, the U.S. Food and Drug Administration, may not be the only agency to have accelerated approval programs, however, it is the only agency to have approved two ADCs through the accelerated approval processes still on the market today.

Third, out of the three agencies that were discussed in this chapter, even though the China Food and Drug Administration is still new and uprising and continually improving their ADC research, it is the cheapest agency to approve an ADC conducting both clinical trials and the administration in China. In addition to the evaluation of strictest policies for the approval process of ADCs, the case studies mentioned at the end of this section emphasize a serious point in the importance of maintaining good laboratory practices (GLPs) as well as developing and adhering to a quality set of standard operating procedures (SOPs). Although the specific details remain unknown, it is clear that Centocor did not adequately uphold the GLPs and SOPs. The next chapter explains our conclusions and recommendations for this report.

Chapter 5: Conclusion and Recommendations

In this chapter, we provide a summary of our key findings and provide recommendations for companies entering into the drug approval process with an antibody drug conjugate. Through our field work, we gained a deeper understanding of the approval process as a whole and what is required of the research companies. We analyzed three major qualities that determined the successful approval of an antibody drug conjugate. We believe that our recommendations can help companies understand the approval process and what is required of them in a coherent way. This chapter concludes with the suggested collaboration of the three agencies to collectively improve the drug approval process.

5.1. Project Summary

The intent of this project aims to provide readers with a summarized comparison of the federal drug regulations of the U.S., China, and the European Union specifically relating to the approval of antibody drug conjugates. Our team focused on three key points: the cost of approval, the length of the approval process, and the level of required safety precautions. We concluded that there is no agency provides "the best" approval process, however, we found that the FDA, EMA, and the CFDA each accommodate to a company's specific interests.

The Safest Approval Process

After examining the rules and regulations of all three approval processes, we conclude that the EMA provides the best drug approval process for a company seeking to maximize the safety precautions for the approval of their drug. Unlike the FDA, where when approved the ADC will remain on the market until it is deemed unsafe or harmful to the public, the EMA will award a one-year marketing authorization which can be renewed. Even a normal drug approval by the EMA licenses the company to market their drug for only five years. This may be particularly attractive

and feasible for large and powerful pharmaceutical companies with funding enough to last through a slightly longer and potentially more rigorous approval process. That said, smaller companies should not immediately arrest consideration of the EMA as a means of initially approving a drug. Safety, both during clinical trials and once on the market, is vital and the EMA provides a relatively safer means of approving an ADC than the FDA or the CFDA. If not upheld, a company's credibility and marketing profits will greatly suffer.

The Fastest Approval Process

Conducting our analysis of the three agencies, we discovered both the FDA and EMA have accelerated approval processes. On average the FDA accelerated approval program takes about eight months to approve an ADC from submission to active market, the EMA takes a little longer at 14 months. A Category 1 CFDA approval estimates a review period of 7-12 months, but the lack of ADCs approved in China is a dissuading factor. Time is always money and in some cases time is everything. For a small biotech or pharmaceutical company looking to approve a monoclonal antibody, an additional year or two in the approval process cannot be spent. Time is also important when companies want to market their drug before competitors. In these cases, biotech and pharmaceutical companies may want to consider seeking approval through either the U.S. FDA's or the EMA's accelerated approval programs. If a company decides to request expedited approval, they then have to struggle with the resulting cost.

The Least Expensive Process

The cost for a drug application is an important factor to manufacturers deciding where to market their drug. There are many types of fees for the three regulatory agencies. The US FDA has an application, establishment, and product fees. The EU EMA has a marketing authorization application fee, extension, variation, and annual fees. The CFDA does not have any major fees

except for those that are required for their providence. With relation to our sponsor, the CFDA offers waivers to small businesses which provide an incentive to the CFDA application process. As a price comparison with the FDA, the FDA's single application fee is 79 times more expensive than the CFDA market-authorization fee. Out of the three agencies, even though the China Food and Drug Administration is still new and uprising and continually improving their ADC research, it is the cheapest agency to approve an ADC conducting both clinical trials and the administration in China.

What We Can Learn from Case Studies

The case study of Centoxin serves to emphasize the importance of maintaining good laboratory practices (GLPs) as well as developing and adhering to a quality set of standard operating procedures (SOPs). Although the specific details remain unknown, it is clear that Centocor did not adequately uphold the GLPs and SOPs. The first time the FDA requested additional information because unauthorized personnel had been allowed to see the data. This problem could have been avoided if Centocor had carefully observed the hierarchy laid out in GLPs. The SOPs should have clearly defined the length of patient observations and the methods used to account for patients who did not provide follow-up data. Centocor either failed to define methods to deal with these important issues or failed to follow through with their SOPs. In the end, the data was so badly mangled that statisticians could not accurately interpret the data and they abandoned the drug.

5.2. Limitations of This Study

A significant issue encountered while conducting the literature reviews previously discussed was the lack of information presented by the CFDA. The agency was only formed recently and the major language of China is Mandarin. Having limited information because of the

age of the agency and access to the information because they were presented in Mandarin contributed to the limitation of our study. Additionally, our team decided to contact experts including various agency officials and experts from academia and industry. We carefully selected authors whose work we had read and emailed each expert a brief, semi-structured interview specifically tailored for the interviewee based on their article. However, many contacts referred us back to their website for more information or did not reply altogether. The limited time to gather data from sources other than databases, articles and journals proved to be difficult as most experts in this field are difficult to contact.

5.3. Recommendations for Future Research

From our analysis of the FDA, EMA, and CFDA approval processes, we recommend that for further development of this project, collaboration with leading drug approval agencies around the world to develop a unified approval and submission process for drugs. Our research shows many similarities between each agency's required submission documents. If there was a single submission format that was accepted by all agencies, the drug approval process for drug development companies would be greatly simplified. This would allow research companies to have the option to view the materials and standards required for submitting their drug. This method would also allow the company more opportunities for submissions worldwide with only one set of submission materials. Overall, this would make a unified drug approval document submission pipeline and drastically reduce the overhead associated with developing multiple sets and formats of submission documents.

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Appendix A: Interview Question Template

Are there major differences in the drug approval process in China and Europe compared with the US? And if so, what are they?

What can speed up or slow down the approval process?

What is the estimated monetary cost to get a drug approved?

How long is the typical process for ADC and therapeutic antibodies?

How do the drug regulations of the FDA, EMA, and the CFDA provide the best safety precautions for the consumers?

Are there any special programs in these agencies that specifically give attention to the approval of a therapeutic antibody or an ADC?

If you were looking to approve a new ADC, which country's market would you target first and why?

Appendix B: OECD Definitions

Good Laboratory Practices

Good Laboratory Practice (GLP) is a quality system concerned with the organization process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported.

Terms Concerning the Organisation of a Test Facility

Test facility: the persons, premises and operational unit(s) that are necessary for conducting the nonclinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered test facilities.

Test site: the location(s) at which a phase(s) of a study is conducted.

Test facility management: the person(s) who has the authority and formal responsibility for the organization and formal responsibility for the organization and functioning of the facility according to these Principles of Good Laboratory Practice.

Test site management: (if appointed) the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these Principles of Good Laboratory Practice.

Sponsor: an entity which commissions, supports and/or submits a nonclinical health and environmental safety study.

Study Director: the individual responsible for the overall conduct of the nonclinical health and environmental safety study.

Principle Investigator: the individual who, for a multi-site study, acts on behalf of the study director and has defined responsibilities for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principle Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles of Good Laboratory Practice are followed.

Quality Assurance Programme: a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice.

Standard Operating Procedures (SOPs): documented procedures which describe how to perform tests or activities normally specified in detail in study plans or test guidelines.

Master Schedule: a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

Terms Concerning the Non-Clinical Health and Environmental Safety Study

Non-clinical health and environmental safety study: (henceforth referred to simply as "study") an experiment or set of experiments in which a test item is examined under laboratory conditions or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.

Short-term study: a study of short duration with widely used, routine techniques.

Study plan: a document which defines the objectives and experimental design for the conduct of the study and includes any amendments.

Study plan amendment: an intended change to the study plan after the study initiation date.

Study plan deviation: an unintended departure from the study plan after the study initiation date.

Test system: any biological, chemical or physical system or a combination thereof used in a study.

Raw data: all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm, or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognized as capable of providing secure storage of information for a time period as stated in section 10, below.

Specimen: any material derived from a test system for examination, analysis, or retention.

Experimental starting date: the last date on which data are collected from the study

Study initiation date: the date the Study Director signs the study plan.

Study completion date: the date the Study Director signs the final report.

Terms Concerning the Test Item

Test item ("control item"): any article used to provide a basis for comparison with the test item.

Batch: a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.

Vehicle: any agent which serves as a carrier used to mix, disperse, or solubilize the test item of reference item to facilitate the administration/application to the test system.

Appendix C: Past Approval Updates

Medicine must constantly change and evolve to keep up with diseases that also change and evolve. Hangzhou DAC Biotech wanted to know how ADCs have changed since their initial market approval and possible lessons learned. The three ADCs that have ever received market approval from either the FDA or EMA (CFDA has not approved any) are Mylotarg, Adcetris, and Kadcyla.

Mylotarg, Gemtuzumab Ozogamicin, was granted Accelerated Approval by the FDA and Orphan Designation by the EMA and approved in 2000. By process of an accelerated approval in any form, post clinical trials are required to verify all statements made. According to the FDA'd article about Mylotarg's withdrawal from market, a post clinical trial conducted in 2004 found that "improvement rates were 66% (150/277) on the Mylotarg plus chemotherapy arm and 69% (159/229) on the chemotherapy alone arm" Additional statistics included a higher toxicity level in "Mylotarg, 5.7% (16/283) versus 1.4% (4/281) for patients receiving chemotherapy alone." The reasoning was found to be that Mylotarg's linker technology allowed the cytotoxic payload to be released prematurely (Gemtuzumab Ozogamicin, 2015).

Adcetris was approved in 2011 to treat two types of lymphoma, and was since then no longer used as a frontline treatment. Chemotherapy was still the initial option for patients suffering from those two types of lymphoma. In 2012, phase I of post clinical trials revealed that the use of Adcetris and Belomycin and had increased the risk of pulmonary lung toxicity (FDA Drug Safety Communication, 2012). As a result, the drug label had to include this warning. After the conclusion of post clinical trials in 2015, Adcetris had been allowed frontline treatment to Hodgkin Lymphoma patients after a transplant becoming the first and only consolidation treatment option

available to high-risk classical Hodgkin lymphoma patients who undergo a transplant to preserve their post-auto-HSCT remissions (Seattle Genetics, 2015).

Kadcyla was approved in 2013 to treat late-stage metastatic breast cancer not used as a frontline treatment. Patients receiving Kadcyla must have received trastuzumab and taxanes previously. In the EMA and FDA, there have been no post approval updates concerning Kadcyla. After studying how approved ADCs have changed, the main lesson to take away is that statistics mean everything, especially for either clinical benefit or damage. The Mylotarg and Adcetris, statistical figures include improvement rates, progression-free survival, hazard ratio, and toxicity level all matter. These figures are known as clinical endpoints. (Clinical Endpoints: Advantages and Limitations, 2015). As diseases change, so must medicines. When making changes to medicines, previous ADCs have used clinical endpoints to be primary evidence for their change.

Appendix D: Bringing a Foreign Drug into China

The CFDA policies are very similar to the policies of the FDA. According to *Optimizing Drug Regulation in China* by PPD, if you are approving a drug in China, it is best to make China the first market to introduce the drug. This is because of the policies on the Category I drug in China. In order for a new drug to be classified as a Category I drug, it must be first submitted for approval in the CFDA before any other agencies. If the drug, is already approved in another agency, clinical trial data from China must be given to the CFDA. Otherwise, the drug must undergo clinical trials in China. This type of drug is called a Category III drug in China. Another requirement of CFDA drugs is that they must be manufactured in China. In summary, the important items about releasing a drug into the Chinese market are having clinical trials conducted in China and having the drug manufactured in China.

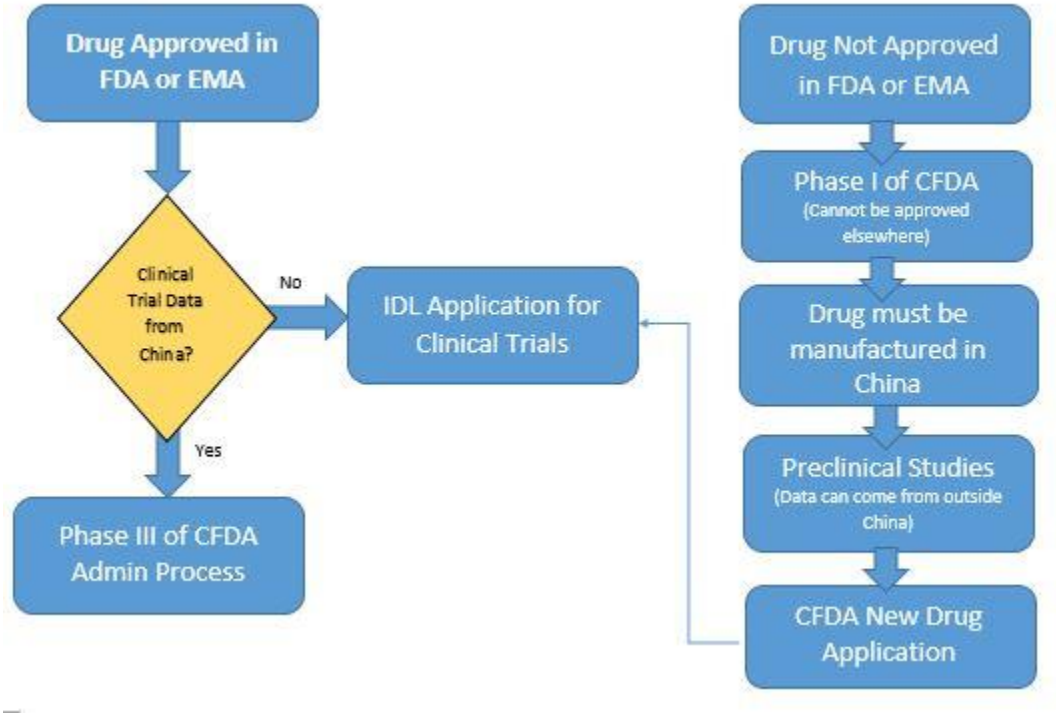

Figure 2: Foreign drug approval process coming into China

Appendix E: New Zealand's Drug Approval Application Process

New Zealand's drug regulatory agency is called Medsafe. Although Medsafe does not oversee drug regulation for such a large population size as compared to the FDA, EMA, or CFDA, it is still a respected drug regulation agency. Hangzhou DAC Biotech wanted a quick overview of Medsafe and how it compared to other the three agencies.

When applying for a New Medicines Application, Medsafe provides guidance documents, which troubleshoot every question in detail, similar to the EMA and FDA (Medicines, 2015). When making claims, only evidence from clinical trials or robust scientific peer review literature can be used. A unique element of Medsafe's application process is that there must be data to show the quality of the product during its shelf-life.

A foreign applicant to New Zealand has to go through some additional steps to meet application requirements as compared to a domestic applicant. Firstly, the applicant must adhere to New Zealand's Good Manufacturing Practices. Although New Zealand's GMPs might overlap with the ones already in place in the applicant's country, Medsafe is only concerned with adherence to New Zealand's GMP. Secondly, the applicant must have a sponsor with a physical address who is responsible for placing the product on the market for you. New Zealand Customs Service can help with the import of the applicant drug (Medsafe has no jurisdiction to deal with controlled drugs at the border.) As defined on New Zealand's Medicines Control website, Medicines Control is responsible for issuing import and export licenses for commercial consignments of controlled drugs pursuant to section 8 of the Misuse of Drugs Act 1975 and regulations 3 and 7 of the Misuse of Drugs Regulations 1977 (Medicines, 2015).

When comparing Medsafe's time to evaluate an application with other regulatory agencies, Medsafe response is line with the EMA. According to Medsafe's website, "[Medsafe] aims to complete its initial evaluation within 200 calendar days of receipt of the application. The total time taken to reach a final decision can vary and depends on the amount and complexity of the information provided and how long it takes the company to respond to Medsafe's requests for more information." In comparison, a regular EMA marketing authorization application is 210 days. The FDA's standard review lasts 10 months.

Medsafe's cost for applications depends on the risk of the medicine. Since ADCs contain one or more active substances, it is considered for the most expensive, high-risk application. At the time of this project, 1 New Zealand Dollar is equivalent to $0.65 US Dollar. Converted from NZ Dollar to the US, a high-risk medicine application costs $58,118 (Medicines, 2015). This price sits near the CFDA in cost.