Policy analysis of foreign trials needed for FDA-approved INDs for devices and drugs from 2016 to 2020

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Policy Analysis of Foreign Trials Needed for FDA-Approved INDs for Devices and Drugs From 2016 to 2020

by

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Thesis

Submitted to the School of Health Sciences
Eastern Michigan University
in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE
in
Clinical Research Administration

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March 1, 2022
Ypsilanti, Michigan
Acknowledgments

I would like to acknowledge Dr. Michael Switzer for guiding me through successfully completing this thesis. His inspiration and immense knowledge in the field of clinical research has increased my interest in the biotechnology field. I would also like to express my gratitude to my biggest supporter, Jacob for always being there for me throughout this degree.
Abstract

Any new drug or medical device requires testing before it can be commercialized. Although there are many paths a product can follow during preclinical testing to bringing it to the market, the need for multinational data is more necessary for drugs in comparison to medical devices. Since drugs do not always need additional data, there is a need to investigate why medical devices are more easily approved than drugs. The use of foreign data is fairly recent, and even though there are advantages to executing clinical trials in foreign countries, some companies do not want to run their studies outside the US. For this study, approved drugs and medical devices were taken from clinicaltrials.gov and the FDA’s website from the years 2016 to 2020 to show the relationship of medical devices approved without the use of multinational data compared to drugs. Although there were more medical devices approved by the FDA without the use of foreign data, the impact of foreign clinical trial data needed for drug and medical device approval long term remains unknown.
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Introduction

To sell a drug or medical device in the United States, companies must test it. The drug development process needs to be approved by the U.S. Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) and the device development process needs to be approved by the FDA Center for Device and Radiological Health (CDRH), both of which are federal agencies that oversee the safety and efficacy of drugs and devices that are being tested. If a product passes the preclinical development stage successfully, an investigational new drug (IND) application needs to be submitted. The product’s sponsor, who is usually the manufacturer or potential marketer, will submit the application explaining why an unapproved product needs to be tested with an outline of the study design the sponsor plans to implement if approved. The FDA’s reviewers may advise for an additional foreign clinical trial if the patient population or indication the unapproved drug will target cannot establish proof of concept without additional data outside of the US population.

Due to medical device and drug development being globalized, many products are not approved if the sponsor did not execute their clinical trial in more than one country. Under the 510k regulation, many medical devices are approved to be marketed in the US without additional foreign trial data. This regulation has resulted in most approved devices being marketed in the US without the need for additional global data. Given that many drugs do not receive FDA approval without multinational data, there is a need to investigate why devices are more easily approved in the US in comparison with investigational drugs.
Background

**Drug and Medical Device Approval Process**

The FDA requires that a drug not be transported across state lines unless it has an approved marketing application. Because a sponsor wants to test the product in multiple states, submitting an IND is a way to get around that legal requirement and become exempt. The IND serves as proof that the drug or device successfully passed preclinical development by showing safety data that gives reasonable proof the product will not “expose humans to unreasonable risk when used in limited, early-stage clinical studies” (Center for Drug Evaluation and Research, 2021, paragraph 2). The application explains the need to research the unapproved drug targeting a new indication or patient population and includes data from animal pharmacology and toxicology studies, manufacturing information, clinical protocols, and the investigator information. This information not only shows that the drug or device is safe for initial testing in humans, but additionally, it includes evidence the manufacturer can produce the product in consistent batches, the qualifications of the personnel who will be testing the product, and protocols that indicate minimal risks for human subjects. The submitted protocols for potential human subject trials will be reviewed by the FDA, who has 30 days to respond and recommend any actions that will assist the applicant in a smooth transition throughout each clinical trial to eventually receive approval to market the product.

The sponsor needs to submit a New Drug Application (NDA) to receive approval to market the product commercially. This application includes data from the IND and additional data gathered from the human clinical trials that is intended to convey the reviewer the product is safe and effective, and the benefits of the drug or device outweigh the risks. In addition, it also contains the product’s proposed labeling and the manufacturing methods that maintain the drug’s
quality is adequate to preserve the product’s identity, strength, quality, and purity (Center for Drug Evaluation and Research, 2022, paragraph 2). After the FDA reviews the NDA, they should know the product’s whole story, from the development process to the current data available.

Global clinical trials are needed and, at times, requested by the FDA because of their need for research studies show data from varied populations. Having data from different geographical sites can convey the product works in the same way in varying ethnic groups (Lang & Siribaddana, 2012, paragraph 3), and starting clinical trials in different countries can result in sponsors not only having data from underrepresented countries, but it can also lead to those subjects benefiting from the investigational product and, overall, improving the health of that community.

Medical devices are easier to market without foreign trial data because of the 510(k)-clearance regulation. If a sponsor would like a medical device marketed in the US, the process would be the same as discussed in the previous paragraphs unless the device is already marketed in another country or the sponsor has a device that is similar to a medical device that is already marketed in the US. To do this, the sponsor would have to submit a 510(k) application. This is a premarket submission that communicates to the FDA their medical device is “as safe and effective, that is, substantially equivalent (SE) to a legally marketed device” (Center for Drug Evaluation and Research, 2020, paragraph 3) along with evidence that supports this claim. The submitter needs to receive communication from the FDA stating that the device is SE to legally market the product.
**Foreign Clinical Trials Background**

Until about 60 years ago, it was uncommon for sponsors to submit data from foreign clinical trials. When President John F. Kennedy signed the Kefauver-Harris Amendments into law in 1962, the FDA not only needed proof of safety to approve a drug or device, but proof of efficacy was needed as well (Green & Podolsky, 2012). In 1975, guidance that permits the submission of foreign clinical trials (FCTs) data that was not conducted under an IND were mapped out in Title 21 of the Code of Federal Regulations Part 312.120 (21CFR312.120) and, as a result, lead to medical device and drug development going global (Office of the Federal Register, 2019, p.86).

Implementing FCTs in the discovery and development of a medical product has posed solutions to obstacles within a regional or local clinical trials. The advantages of running an FCT can include overall reduced costs, finding treatment-naïve subjects eager to participate, a large pool for subject recruitment, faster recruitment, and therefore, a shorter timeline for a clinical trial (Ayalew, n.d., paragraph 5). To further understand the advantages FCTs offer and why sponsors are going global with their clinical trials, a comprehension of the FDA drug and medical device approval process must be understood.

**FDA Drug Review Process**

Sponsors and investigators who are using a pharmaceutical drug that has not been approved by the FDA need to submit an IND for approval. This process is to evaluate the safety and efficacy of the product, and if the regulation is not followed, it could result in legal and financial consequences for the study personnel involved.

The IND application allows the FDA to review the investigational drug at hand within the respective department, usually CDER or the Center for Biologics Evaluation and Research
(CBER): “Most pharmaceutical drug products, both synthetic and biologic, fall under the regulatory supervision of CDER, including most drug studies” (Holbein, 2009) while CBER oversees products such as vaccines and allergenics. The original federal laws that the FDA follows are found within the Federal Food, Drug, and Cosmetic Act within the Code of Federal Regulations (CFR) in Part 312 (Office of the Federal Register, 2019, p.53). Due to the IND containing the information needed to test the investigational drug on humans, it needs to have enough safety data showing it will not cause undue risk for subjects in the potential study. An IND should be submitted for any investigational drug that has not been marketed, including approved drugs aimed at unapproved indications, new formulations, new doses, or new patient populations (Holbein, 2009).

Once the IND application is submitted, the sponsor should expect to receive a letter from the FDA confirming the receipt of the IND application. Once the letter is received, the sponsor will need to wait 30 days before initiating their clinical trial. If the clinical trial does not meet the FDA’s safety standards, a letter will be sent to the sponsor putting the clinical trial on complete or partial hold. A partial hold means that a part of the study cannot begin, and a complete hold means that the study cannot be initiated (Holbein, 2009, paragraph 3). If the FDA’s discretion is to hold the study, the investigator will be told the reasons by telephone, followed up with a letter stating the issues cited. The sponsor then can address the concerns by sending another letter and will need to wait 30 days for the FDA to respond. If a response is not received in that timeframe, the sponsor can proceed to being their clinical trial. After the clinical trial starts, the sponsor is responsible for notifying the FDA if there are “any additional safety issues, file annual reports, and to notify the FDA when the study ends for any reason” (Holbein, 2009, paragraph 2). Overall, it is the sponsor’s duty to file and maintain the IND application.
The next step is to file a marketing application, but a sponsor must have sufficient data from two large, controlled clinical trials. If the company has this information, the sponsor will need to file an NDA to market the drug. Since this application tells the whole story of the investigational drug, it needs to show that the product is safe and effective for the intended patient population. This information should include safety updates, proposed labeling, drug abuse information, patent information, directions for use, institutional review board (IRB/IEC) compliance information, and any data from studies that may have been conducted outside the United States (Office of the Commissioner, 2018c, paragraph 3). If the NDA is incomplete, the FDA will not file the investigational product.

Approving the NDA can take 6-10 months because of the due diligence that needs to be complete. This includes the members of the review team conducting a full review of their section as well as FDA inspectors traveling to clinical study sites to confirm there is not fabrication, manipulation, or withholding of data (Office of the Commissioner, 2018c, paragraph 1). The project manager puts together all individual reviews and other documents into an “action package”. This package will be reviewed by the FDA team and a senior FDA official makes the final decision on whether the investigational drug is approved or not.

**FDA Device Review Process**

The development process for medical devices depends on the device’s classification. There are three different classifications for a device and the class could change based on the results of a study: “FDA classifies medical devices based on the risk posed by the device” (Office of the Commissioner, 2018a paragraph 1).

Class 1 devices create the least amount of risk and must adhere to “general controls”. General controls examine good manufacturing practices, standards and reporting adverse events
(AEs) to FDA, registration, and general recordkeeping requirements and can include products such as surgical tools and oxygen masks (Office of Commissioner, 2018, paragraph 2).

Class 2 medical devices consider general controls and special controls because of their increased risk in comparison to Class 1 devices. Along with being subject to general controls, special controls encompass labeling requirements, device specific mandatory performance standards, and device-specific testing requirements (Office of Commissioner, 2018b, paragraph 3).

Class 3 medical devices pose the most risk and are intended to sustain life, are implanted in the body, or present unreasonable risk of illness or injury. These devices need premarket approval, and to receive approval, manufacturers must prove that the device is safe and effective. Class 3 devices can include pacemakers and implants, but each device needs to show proof of concept in the beginning stages of development, no matter the classification.

To show that a medical device works, researchers first need to build a prototype. This process is not tested on human and normally changes several times with the intended result of reducing risk for people. Once the research team can prove the device’s safety and effectiveness, an application to market the product can be filed. Similar to how devices are classified differently, they should also be filed differently.

Class 1, 2, and 3 devices are filed under the premarket notification, also known as 510(k). This specifies that the product that is being filed is like another medical device that is already on the market. To do this, the developer needs compare their device to an already legally marketed device.

Class 3 devices can also be filed under a premarket approval application (PMA) if a 510(k) is not required. This application must include both the nonclinical and clinical data:
“During the approval process, FDA will inspect the manufacturing laboratories and facilities where the device will be made to check for good manufacturing practices” (Office of Commissioner, 2018d, paragraph 4). Just like the drug approval process, the FDA may consult an advisory committee during a public meeting. This committee consists of experts who provide advice on different investigational products. Since their advice are recommendations, the committee does not make the final decision on whether the product is approved. After the committee discusses their recommendations with the FDA, the FDA can either approve it or request additional information.

Once the device is on the market, the FDA will continue to monitor the product since new safety concerns could be discovered while the public uses it. Monitoring includes manufacturing inspections and several programs that allow the public to report problems with the product. FDA officials conduct manufacturing inspections of the facilities that produce the product. The manufacturers may be informed of the inspections in advance, or they may take place unannounced (Office of Commissioner, 2018e, paragraph 6). The inspection could be initiated because of a problem with the product, but it could also take place as a routine inspection. The intention is to keep manufacturers practicing good manufacturing, but the FDA can shut a facility down if it does not meet their standards.

Along with routine inspections, the FDA provides several programs that allow health professionals and consumers the ability to report an issue. MedWatch, the FDA’s adverse reporting program, is a system that that tracks reporting problems for both drugs and devices. This system also can alert the public to new safety information that has been reported about specific products. Medical Product Safety Network (MedSun) is another program that tracks reported issues for products as well as monitoring a product’s safety and effectiveness: “FDA
recruits 350 healthcare providers throughout the US to report any medical device problems that result in serious injury or death” (Office of Commissioner, 2018d, paragraph 4). Although safety alerts cannot be requested for this program, MedSun publishes a newsletter each month that discusses important information about medical device safety. The FDA is also working on developing a new program that actively surveys issues, the Sentinel Initiative: “The system will use very large existing electronic health databases—like electronic health records systems, administrative and insurance claims, and registries—to keep an eye on the safety of approved medical products in real time” (Office of Commissioner, 2018d, paragraph 5). This system will help FDA officials monitor postmarket safety.

**Premarket Approval Notification vs. Premarket Notification 510(K)**

Since devices are placed into a class based on their risk, FDA officials need to ensure safety and efficacy. All Class 3 devices are required to meet premarket approval application (PMA) requirements. Like an NDA, the PMA needs to be approved by the FDA CDRH to have a private license and market a medical device. All approved PMAs are available on the FDA’s website and include the following information:

- classification name,
- generic name,
- applicant,
- PMA number,
- supplement number,
- trade name,
- date received,
- decision date,
- product code,
- advisory committee,
- supplement type,
- supplement reason,
- expedited review granted (yes or no), and
- approval order statement (CDRH, 2021).

Because Class 3 medical devices support or sustain life, a review of general and special controls are insufficient for FDA approval. Thus, Class 3 devices are requiring a PMA under section 515 of the FD&C Act to obtain marketing approval (CDRH, 2019a, paragraph 3). This PMA is intended to show that the device is both safe and effective for the intended use. The majority of PMAs feature new concepts and are not a type of device that is already marketed: “If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it could impact the FDA’s review and approval” (CDRH, 2019a, paragraph 2). There are several guidance documents regarding PMAs on the FDA’s website, including PMA regulations, frequently asked questions, and special considerations (CDRH, 2019a, paragraph 3).

In contrast, a premarket notification is needed if the medical device does not require a PMA. Although there is not a specific 510(k) form, 21 CFR 807 Subpart E describes the requirements needed (CDRH, 2020, paragraph 2). Before a sponsor can market a medical device, they must receive a letter stating that the FDA finds the device to be substantially equivalent and can be marketed in the US. This means that the medical device is not only safe and effective, but also is substantially equivalent to a legally marketed device. Once a company submits this information, the FDA will decide if it can be approved for marketing within 90 days. A device is substantially equivalent if, in comparison to a predicate, it
- has the same intended use as the predicate; and
- has the same technological characteristics as the predicate or
- has the same intended use as the predicate; and
- has different technological characteristics and does not raise different questions of safety and effectiveness; and
- the information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device (CDRH, 2020, paragraph 4).

The performance data needed can include clinical data and non-clinical bench performance data, engineering performance testing, and software validation. There are four categories of parties that must submit a 510(k):

- domestic manufacturers introducing a device to the U.S. market,
- specification developers introducing a device to the U.S. market,
- repackers or relabelers who make labeling changes or whose operations significantly affect the device,
- foreign manufacturers/exporters or U.S. representatives of foreign manufacturers/exporters introducing a device to the U.S. market (CDRH, 2020, paragraph 3)

**Investigational Device Exemptions**

If a company wants to test an investigational medical device in order to show safety and efficacy, the IDE allows the company to do so. This can also include the evaluation of specific modifications or a new intended use. Furthermore, all clinical evaluations of medical devices must have an approved IDE before the study is initiated. Clinical evaluation of device that have not been approved for marketing must include
• an investigational plan approved by an IRB. If the study involves a significant risk, the IDE must also be approved by the FDA;
• informed consent for all patients;
• labeling stating that the device is for investigational use only;
• monitoring of the study; and
• required records and reports (CDRH, 2019a, paragraph 2).

The IDE permits investigational medical devices to be shipped, stating that the intent is for investigational use in compliance with the Food, Drug, and Cosmetic Act (FD&C Act), which establishes quality standards for food, drugs, medical devices, and cosmetics manufactured and sold in the US (Office of the Commissioner, 2019, paragraph 1). Companies do not have to submit a PMA or 510(k) and are exempt design controls requirements from the Quality System (QS) regulation.

**FDA Guidance for Foreign Clinical Trials**

The current law governing FCTS are found in 21CFR312.120. This states that a sponsor does not have to conduct an FCT under an IND to use it as supportive data for an NDA, IND, or IDE. However, if a study is conducted outside of the US under an IND, then that company must still follow the necessary FDA regulations just like a clinical trial in the US would be executed. This includes the study being conducted in accordance with good clinical practice (GCP), an FDA standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides the assurance that the data is accurate, and the rights and well-being of human subjects were protected (Office of the Federal, 2019, p.86). This information that needs to be submitted should also include the following: the investigator’s qualifications, description of the research facilities, summary of the protocol and
results of the study, a description of the medical product, and a summary of the IEC’s decision and member qualifications (Office of the Federal Register, 2019, p.86-87). It should also include details on how the informed consent is obtained, how the sponsor monitored the study, and how the study personnel were trained.

Furthermore, there is specific guidance the FDA provides on the acceptance of foreign clinical studies not conducted under an IND. This can be found on the FDA’s website and includes instruction on GCP regulations and how to receive approval from IECs so that sponsors and other applicants submit their information in a consistent and standardized manner that demonstrates compliance with regulations in 21CFR312.120 (U.S. Department of Health and Human Services, 2012, p.2). This helps sponsors navigate carrying out an FCT and the challenges and advantages that many companies face in doing so.
Chapter 2: Analysis and Methods

Purpose of the Analysis

To gain a better understanding of how many FCTs are conducted for medical devices in comparison to investigational drugs, an analysis must be carried out. For the purpose of the analysis, data was included for a 5-year timespan on medical devices and drugs that were approved by the FDA from years 2016 to 2020.

Methodology

A literature search was conducted on government websites that obtains clinical study summary information reports on clinical trials both in the US and with FCTs. These websites include www.ClinicalTrials.gov and the FDA’s official website, www.FDA.gov. This was done by navigating to the FDA’s website, FDA.gov, and searching for device or drug approvals for a certain year. Once taken to the approvals page, each device or drug was clicked on and from there, the user can click on the Summary of Safety and Effectiveness Data (SSED). The user can then see which countries carried out the product’s clinical trial (Office of Commissioner, 2020, paragraph 8). From these reports, data was collected on whether the clinical trial was a multinational study. This information can also be found on clinicaltrials.gov. This was carried out by navigating to clinicaltrials.gov and searching for the product. From there, the user can see which countries carried out the product’s clinical trial. The intention of the methodology is to show significant trends in the approval of overall studies that were approved vs. studies that had an FCT. This is also shown as a percentage of multinational clinical trials vs. domestic clinical trials.
Chapter 3: Results

Part 1: Overview of Approved Drugs From 2016 to 2020

Figure 1

*Approved Drugs from Years 2016-2020*

According to the FDA and www.ClinicalTrials.gov, the number of drug approvals that feature a clinical trial component has been consistent over this 5-year timespan. Figure 1 shows the increase in the reliance of multinational clinical trials for the first three years and a slight decrease for the last two years.
Figure 2

Drug Approvals From Years 2016 to 2020

Figure 2 reflects the data in Figure 1. This shows the trends of the number of drug approvals increasing and then decreasing over a 5-year timespan.
Overview of Devices Approved From 2016 to 2020

Figure 3

Approved Medical Devices From Years 2016 to 2020

According to the FDA and www.ClinicalTrials.gov, the number of medical device approvals that include a clinical trial component has been inconsistent over this 5-year timespan. Figure 3 shows the decrease in the reliance of multinational clinical trials for the first two years, an increase in the third year, and a decrease for the last two years.
Figure 4

Approved Medical Devices From Years 2016 to 2020

Figure 4 reflects the data in Figure 3. This shows the trends of the number of device approvals decreasing, then increasing and back to decreasing over a 5-year timespan.
A Comparison of Approved Drugs vs. Medical Devices

**Figure 5**

*Medical Device and Drug IND Approvals From Years 2016 to 2020*

Figure 5 shows a comparison between the number of approvals overall as well as a focus on how many of those trials had a foreign trial component, according to the FDA and www.ClinicalTrials.gov. Overall, there were more drug approvals than medical device approvals. Furthermore, the number of drug approvals that featured a foreign clinical trial was more than double the amount of medical device approvals that had a foreign clinical trial.
Figure 6

*Medical Device and Drug Approvals From Years 2016 to 2020*

Figure 6 reflects the data in Figure 5. This shows the trends of the number of approvals over a 5-year timespan. This graph gives a visual representation that displays the magnitude of change for the four different categories over time.
4) Discussion

To commercialize a medical device or drug, companies must test it in different regions or countries based on the indication or patient population the investigational product is targeting. Since clinical trials have globalized, it is common for the FDA to approve an IND or PMA that is filed with multinational data. This not only shows proof of efficacy and safety for subjects in multiple countries, but there are also advantages for sponsors to execute global clinical trials rather than running a study in one country: “According to Center Watch, 86% of US clinical studies fail to recruit the number of subjects on time” (Bansal, 2012, paragraph 2). Due to sponsors not meeting their recruitment goals according to their study design timelines, they are looking to open clinical trials in foreign countries. Recruitment is especially hard for sponsors who target their products at rare diseases or have challenging endpoints, such as oncology indications like non-small cell lung cancer (NSCLC) and extranodal natural killer T cell lymphoma (ENKTL). To mitigate this challenge, sponsors will execute multinational trials so that there are more patients for study sites to approach and faster recruitment can result in a shorter duration of the sponsor’s timeline.

Filing a submission with global data is becoming more common and sponsors are quickly finding out that this not only could increase their recruitment rates, but it could also save companies money. Running clinical trials in foreign countries could be more cost effective than running trials in only the US. A research study center in India is ten times cheaper than a clinical site in the US. Furthermore, when the pharmaceutical industries run their clinical studies in other countries, there is the possibility of investigating different regulatory barriers and achieving market expansion (Eccard da Silva, 2016, p.1).
When sponsors are contemplating whether to have their clinical trials in a different country, they should consider the following: the qualification of the investigators; the number of patients within their target patient population that have access to medical care; intellectual property protection, including patents, copyrighting, and pirating; and the degree of intervention from their government (Eccard da Silva, 2016, p.3). These considerations will make it easier for a sponsor to decide whether to fund a clinical trial in a different country.
Chapter 5: Conclusion

Based on the analysis of the results, it was observed that there is inconsistency on the amount of FDA approvals for both medical devices and drugs. However, there were many more drugs that could not be approved without multinational data in comparison to medical devices. This could be due to the 510(k) and PMA process whereas drugs do not have a similar approval process that can commercialize drugs if another similar drug is already on the market.

From years 2016 to 2020, more drugs were approved (228) in comparison to medical devices (215). As shown in Figure 5, the number of drug approvals that had an FCT was more than double the amount of medical devices approvals that had an FCT. As shown in Figure 4, the number of approved medical devices with an FCT was about half of the number of overall approved medical devices for each year, respectively 26 vs. 19 in 2016, 27 vs. 9 in 2017, 54 vs. 28 in 2018, 46 vs. 17 in 2019, and 62 vs. 9 in 2020. Furthermore, each year did not have a consistent percentage of FCTs in medical device approvals, respectively: 73.1% in 2016, 33.3% in 2017, 51.9% in 2018, 37.0% in 2019, and 14.5% in 2020. Over a 5-year timespan, Figure 3 shows there were almost three times the amount of approved medical devices that did not have an FCT (215) in comparison to the amount that did have an FCT (79). As shown in Figure 1, 86.8% (198) of overall drugs (228) approved from years 2016 to 2020 featured an FCT. Accordingly, each year had a high percentage of FCTs in drug approvals, respectively: 81.8% in 2016, 93.5% in 2017, 89.8% in 2018, 83.3% in 2019, and 83.0% in 2020.

Although there are many advantages to executing clinical trials in foreign countries, there are also many disadvantages and risks that sponsors are not willing to explore. If sponsors and investigators are following GCP regulations and the standards in the CRF, a clinical trial can be completed in any country that is cost effective and has the patient population that can prove the
product’s efficacy and safety. Due to the globalization of clinical trials being a recent trend, the impact foreign clinical trial data needed for NDA approval long term remains unknown.
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