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FDA Clinical Site Inspections: Rates for Foreign Sites vs. Domestic Sites

by

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Abstract

The Food and Drug Administration (FDA) is the regulatory agency that reviews, clinical trials to maintain the integrity and safety of the trials' human subjects. It is noted that over 80% percent of the subjects enrolled in clinical trials were from foreign countries. While foreign trials should follow Good Clinical Practice (GCP) regulations, many errors have been observed that affected the integrity and safety of human subjects. Since 2008, concern over the inspections of foreign clinical trials has increased, as many reports stated that the rate of inspection of foreign clinical trials is less than that of domestic trials. The main focus of this paper was to observe the difference in the rate of inspections of foreign clinical trials compared to domestic trials and also the factors that are responsible for the movement of clinical trials to foreign countries. Data were collected regarding the inspections and analyzed. The frequency of clinical trials increased in foreign countries over the past few years and also the inspections that were conducted at the foreign sites have increased. The percentage of foreign clinical sites and the percentage of clinical site inspections were analyzed over a 7 year period and it was shown that the rate of increase of foreign clinical site inspections matched the rate of increase in foreign clinical sites. The rate of domestic inspections still lags that of international inspections, however. The FDA responded to the issues by stating that they have initiated various efforts, such as amending regulations, increasing foreign inspections, and striving to find the issues that are responsible for the difference in the rate of inspection.

Keywords: Foreign clinical trials, domestic clinical trials, inspections

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Introduction

The Food and Drug Administration (FDA) is a regulatory agency within the U.S. Department of Health and Human Services. The main focus of the FDA is to maintain the safety and effectiveness of drugs sold in the United States. The FDA also plays role in maintaining the integrity of the clinical trial data and also the safety of the clinical trial subjects. The FDA divided the regulatory review phases of clinical trials into premarket and post market processes. The FDA reviews a drug's safety and effectiveness over its time of existence in the market. According to Thaul (2012), the FDA's review process of drugs occurs through four steps:

- Investigational new drug application (IND),
- Clinical trials,
- New drug application (NDA), and
- FDA review.

The drug review process begins with the filing of an IND, after the findings from the laboratory and animal studies. After the IND is accepted, the study drug is eligible to enter into a process of clinical trials, in which phases I, II, and III are conducted to discover the safety and efficacy of the drug. The next step is to file an NDA, and the FDA reviews the drug for its safety and effectiveness before approving it for marketing in the United States (Thaul, 2012).

Inspection is defined as:

> The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (FDA, 1996).

The FDA conduct inspections of clinical trials to maintain the trial integrity and protection of the trials' human subjects.

(Miller [n.d]) the main objectives of a clinical trial inspection are:

- To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials.
- To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications.
- To assess compliance with FDA's regulations governing the conduct of clinical trials.

The FDA faces a challenge in which the inspection rate of foreign clinical trials is less than domestic (i.e., U.S.) clinical trials. Due to the globalization of clinical trials, most of a drug's data are collected from foreign clinical trials, which increase concern over the inspections. Therefore, the FDA is striving to avoid errors, maintain safety, and improve the integrity of the clinical trials. Another concern of foreign trials is to what extent they are conducted according to ethical and regulatory standards, and whether the clinical trials are to be conducted under good clinical practices (GCP; U.S. Department of Health and Human Services [HSS], 2010).

David et al., (2008) reported that the first FDA inspections of clinical investigators initiated in the 1960s, and in the 1970s regulations were designed by the FDA for each of the parties involved in clinical trials. In the 1980s, the FDA began the inspection of clinical investigators and sponsors outside of the United States. In 1997, ICH GCP guidelines were published, which initiated global harmonization. Finally, in the 21st century, the FDA introduced a new rule that states that non-U.S. trials are accepted only when the drugs are in compliance with GCP.

According to Silverman (2010) the concern over the inspection of foreign clinical trials increased as an Office of Inspector General (OIG) report 2008 stated that over 80% of the clinical trials of the approved drugs were conducted in foreign countries and 78% of the clinical trial subjects enrolled in foreign countries. The OIG report also stated that the inspection rate by the FDA in 2008 was 1.9% in domestic clinical trials and 0.7% percent in foreign trials. Thus, all of these factors caused the FDA to focus on increasing the inspection rate of foreign clinical trials.

Purpose of the Study

The main purpose of this paper was to observe the rate of clinical trial inspections by the FDA in foreign countries and to to determine if FDA inspections are keeping up with the move to international sites.

Literature Review

According Ayalew (2013), clinical investigations had increased gradually in foreign countries from 1995-2006.. Figure 1 presents the annual growth of clinical investigations in foreign countries from 1995-2006.

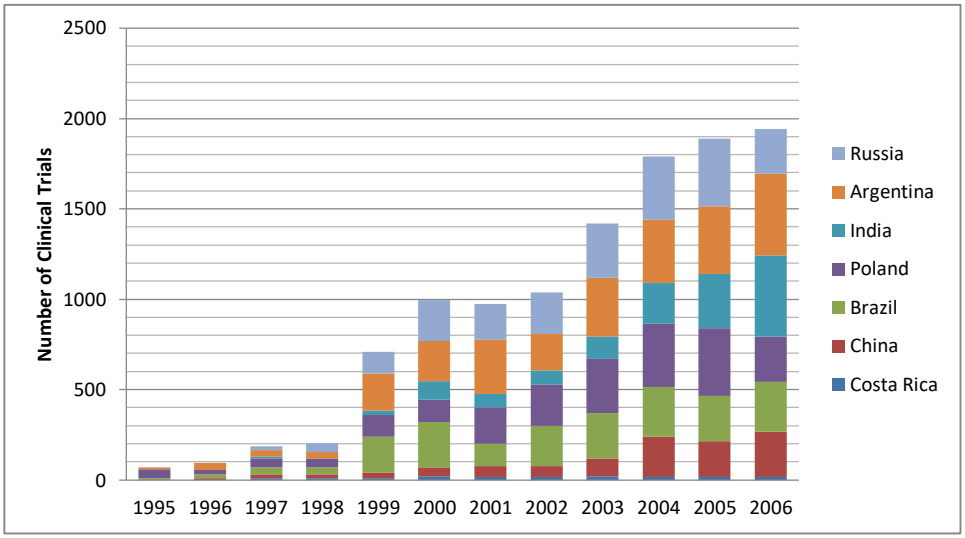

Figure 1 Increasing Annual Growth of Clinical Trials Outside the United States

Adapted from "FDA Perspective on International Clinical Trials" (Ayalew, 2013)

The Department of Health and Human Services (2010) reported that the FDA inspected 1.9% of domestic clinical trials and 0.7% of foreign clinical trials in 2010. The report also stated that:

> Logistical challenges and sponsors' submission of clinical data in a nonstandard format also hinder FDA's ability to monitor foreign clinical trials. FDA was also unable to account for all clinical trial information because application files were missing or the sponsors failed to provide site locations and subject enrollment in the clinical study reports.

After analyzing drug approvals by the FDA in 2008, Karlberg (2009) noted that about 80% of approved clinical trial data were from foreign clinical trials. However, more than half of the U.S. registered clinical trials were not inspected by the FDA.

Gotthelf, McCarter, and English (2010) reported that 40-60% of clinical trials were conducted in foreign countries and 78% of the enrolled subjects were from foreign sites. One third of U.S. companies conducted clinical trials outside U.S. clinical sites. Gotthelf, McCarter, and English (2010) also reported that from 2001-2006, Asia had an increase of 29% in clinical trials and the United States had a reduction of 2.9% in clinical trials.

The Government Accountability Office (2008) reported that the FDA's database has inaccurate information about foreign clinical trials that are to be inspected. The FDA made various improvements in the clinical trial registry database, such as creating unique identification numbers of the drugs imported to the United States.. According to the Alliance for Human Research Protection (2010):

> One big factor in the shift of clinical trials to foreign countries is a loophole in FDA regulations: if studies in the United States suggest that a drug has no benefit, trials from abroad can often be used in their stead to secure FDA approval. There's even a term for countries that have shown themselves to be especially amenable when drug companies need positive data fast: they were called "'rescue countries."

There are several reasons that sponsors are preferring to conduct clinical trials in foreign countries:

- The cost to conduct foreign clinical trials is less when compared to domestic trials (Flaherty et al., 2000);
- Clinical trial participants are reducing in number in domestic trials when compared to foreign clinical trials (Flaherty et al., 2000);

- Developing countries have a high prevalence of certain diseases, which makes it easier to organize clinical trials (Flaherty et al., 2000);
- Developing countries have a diverse population with many diseases, providing the opportunity to test many drugs (Flaherty et al., 2000);
- There is an ability to recruit patients more quickly from an expanded potential subject pool (Flaherty et al., 2000);
- Availability of CROs focusing on global trials (Ayalew, 2013);
- Widespread adoption of the ICH-GCP guidelines and stronger intellectual protections (Ayalew, 2013); and
- Fewer logistical problems, like contracts and bureaucracy, and reduced regulatory barriers (Ayalew, 2013).
- A first-rate academic medical center in India may charge one-tenth the cost a second-tier medical center in the U.S. would charge (Flaherty et al., 2000)
- In addition, patients in developing countries with little exposure to medications make better subjects for clinical testing. For example, India is an appealing country for sponsors to conduct clinical trials because it has a genetically diverse population of over one billion people who have a myriad of diseases, yet has not been exposed to many medications (Nundy et al., 2005).
- Conducting of clinical trials globally will also shorten the timeline for drug development (Glickman et al., 2009).

Though there are advantages to conducting clinical trials in foreign countries, there are concerns about the integrity of data, safety of subjects, and verification of clinical results (Gardiner, 2010). Concerns also exist about the safety of human subjects, mainly where

regulations are not yet enforced (Singh, 2008). For example, multinational companies conducting foreign trials could sponsor unethical trials (Strickler, 2010). The multinational companies employ independent contractors who enroll the patients in the foreign countries and these companies also employ technicians who gather human subjects and conduct clinical trials themselves. The reasons for the lower inspection rate of foreign clinical sites as stated by the FDA (Flaherty et al., 2000):

- Lack of awareness of some ongoing clinical trials;
- Submission of foreign clinical trial data in nonstandard formats;
- Language barriers;
- Time availability and itinerary problems;
- Budget availability
- Unavailability of locations of clinical trials.

A recent study searching the www.ClinicalTrial.gov found that around one third of the twenty largest US based pharmaceutical companies are conducting clinical trials in foreign countries (Glickman et al., 2009)

FDA Regulations on Inspections of Clinical Trials

The regulations for submission of domestic and foreign clinical trial results were framed by the FDA to ensure safety in standards of conducting clinical trials (Ourso, 2012). The FDA has the right to inspect the clinical trials by which drugs will be approved in the United States to ensure that clinical trials follow the necessary regulations. According to the Department of Health and Human Services (2001), the results of foreign and domestic inspections are classified into different types:

- Official Action Indicated (OAI): The FDA takes official action against an investigator (e.g., sends a warning letter outlining any violations and requesting a response or, for more serious violations, refuses to accept data).
- Voluntary Action Indicated (VAI): The FDA asks the investigator to make voluntary changes.
- No Action Indicated (NAI): The FDA's inspection reveals no objectionable conditions or practices; the clinical investigator is not required to make any changes.

The sponsor submits an IND application to the FDA for the study of the new drug in human subjects**.** The IND contains data that are necessary to ensure the safety for human testing**.** After acceptance of the IND application, the sponsor may conduct trials in humans by following the necessary guidelines and regulations framed by the FDA. The domestic clinical trials follow the IND regulations framed by the FDA for the submission of an NDA application; however, it is not mandatory for foreign clinical trials, as sponsors may conduct trials without an IND (HSS, 2010)**.**

To market a drug in the United States, a company that manufactures a drug must obtain a new drug application (NDA) approval from the FDA. For the NDA approval, the sponsor must

submit all necessary data to the FDA that ensures the safety and effectiveness of the drug for the intended indication. The sponsor then gathers all of the clinical trial data together that are necessary for filing the NDA application for the approval of the drug**.** (Human Subject Protection, 2008) As the number of clinical trials in foreign countries is increasing, the FDA has amended the regulations of foreign clinical trials to ensure the integrity of the data and to protect the human subjects. A domestic clinical trial's sponsor should file the IND before initiating the clinical trial, whereas foreign clinical trials may or may not be conducted under an IND. However, even though the foreign clinical trials can be conducted without filing INDs, they should follow the guidelines of the Declaration of Helsinki, Good Manufacturing Practices (GMP) and the local regulations that are specific to each particular location. The FDA then would review the safety of the clinical trials at the time of NDA submission and, if necessary, would inspect the clinical trial sites.

The FDA requires the clinical trials that are conducted under INDs should be registered in an accessible databank, www.clinicaltrials.gov (Food and Drug Administration Amendments Act, 2007) whereas, if the clinical trials were conducted outside the USA and without IND, those trials need not be registered in the database. The Food and Drug Administration Amendments Act (FDAAA) has extended and expanded the clinical trial registration requirements of the databank to include all applicable clinical trials.

The applicable clinical trial is defined as:

> The controlled clinical investigation, other than a phase 1 clinical investigation, other than a phase 1 clinical investigation, of a drug subject to section 505 of federal food, drug, and cosmetics act or in section 351 of food and drug amendments act (Food and Drug Amedaments Act, 2007).

The FDAAA requires that the sponsor who conducts the applicable clinical trial should submit information into the databank no later than 21 days after the first subject is enrolled. The

FDAAA also requires the sponsor to submit the results to the National Institutes for Health for inclusion into the clinical trial registry data bank. The FDA also conducts on-site inspections to ensure that clinical investigators, sponsors, and Institutional Review Boards (IRB) follow the FDA regulations (HSS, 2010). The FDA can inspect both foreign and domestic sites and inspections occur after the marketing application or while the clinical trial is ongoing (Flaherty, Nelson, & Stephens, 2000).

FDA released guidance to standardize the acceptance of foreign clinical trial data that, according to 21 C.R.F. 312.120, the new drug application (NDA) an abbreviated new drug application (ANDA), should comply with GCP regulations and should allow the FDA to inspect on site (Latham et al., 2012). (Investigational New Drug Application, 2013) specified the requirements that sponsors must submit as supporting information for the clinical trials that are not conducted under an IND:

- Investigational qualifications;
- A description of research facilities;
- A detailed summary of the protocol and study results;
- A description of drug substance and drug product;
- Information showing that the effectiveness of the study is adequate and well controlled under 21 CFR 314.216;
- The name and address of the Independent Ethics Committee (IEC) that reviewed the study and a statement that the IEC meets the definition in 21 CFR 312.3 (b);
- A summary of the IEC's decision to approve, modify, and approve the study, or to provide a favorable opinion;
- A description of informed consent obtained;
- A description of what incentives, if any, were provided to the subjects to participate;
- A description of how the sponsor monitored the study and ensured that the study was carried out consistently with the study protocol [312.12 (b) (10)]; and
- A description of how the investigators were trained to comply with GCP and to conduct a study in accordance with the study protocol, and written commitments by the investigators to comply with GCP and the protocol.

Methodology

A literature search was conducted on government organizations that produce reports on the clinical trial inspections. The reports were based on the analyses that were conducted on FDA databases, www.ClinicalTrial.gov and other websites. From these reports, data were collected at the rate of inspections of foreign and domestic clinical trials. The data collected were based on the number of inspections and number of sites of foreign and domestic trials. The percentage of foregin inspections were seen over time for significant trends and the data of the percentage of the NDA studies over time that were conducted overseas for significant trends. Then collected data on the percentage of foreign clinical inspections are compared with the percentage of foreign clinical sites and the data is analyzed to see if the rate of foregin inspections matches the rate of foreign clinical sites

Results

According to HHS (2010), the clinical investigators conducting clinical trials have been increasing for over the past decade. Figure 2 shows the increase in the reliance on the foreign clinical trials for FDA-regulated drugs and illustrates the percentage of clinical investigators conducting foreign clinical trials.

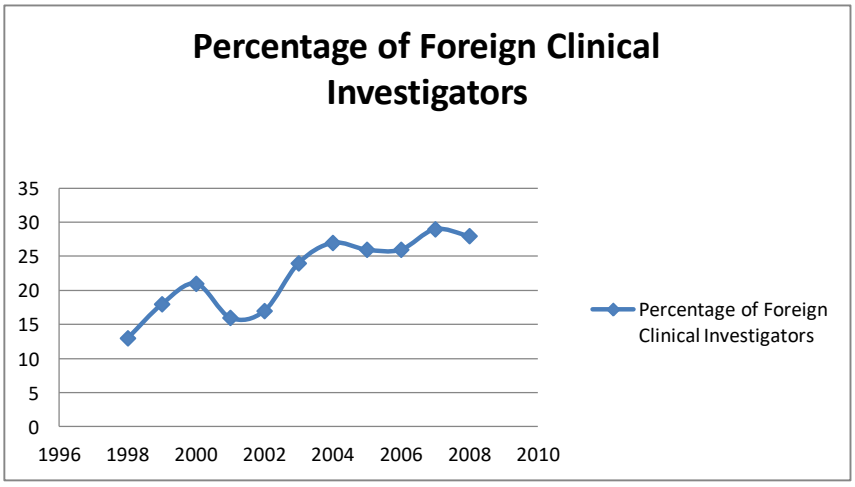

Figure 2 Percentage of All Clinical Investigators Identified in Investigational New Drug Application from 1998 to 2008. Adapted from "Challenges of FDA's Ability to Monitor and Inspect Foreign Clinical Trials" (U.S. Department of Health and Human Services 2010).

The foreign and domestic clinical investigator inspections have been increased from 2002-2009. Domestic Clinical Investigator (CI) Inspections conducted gradually increased from 277 to 458 from 2002 to 2009 and International CI inspections have increased from 37 to 119 from 2002 to 2009. (See Table 1.)

Table 1 Clinical Investigator Inspections (CI) - Domestic and International- FY 2002 - 2009

Year	CI Inspections Domestic	Percentage of Inspections Domestic	CI Inspections International	Percentage of CI Inspections International
2002	277	88.2	37	11.7
2003	368	89.3	44	10.6
2004	351	80.6	84	19.3
2005	366	83.9	70	16
2006	408	80.7	97	19.2
2007	369	78.0	104	21.9
2008	407	82.7	85	20.8
2009	458	79.3	119	21.5

Note. Adapted from Bioresearch Monitoring and Inspections (Tejashri [n.d])

Figure 3 shows the percentage of foreign clinical sites and the percentage of foreign clinical inspections for the years 2002 to 2008 and the slopes of foreign clinical site inspections and foreign clinical sites calculated by the regression analysis.

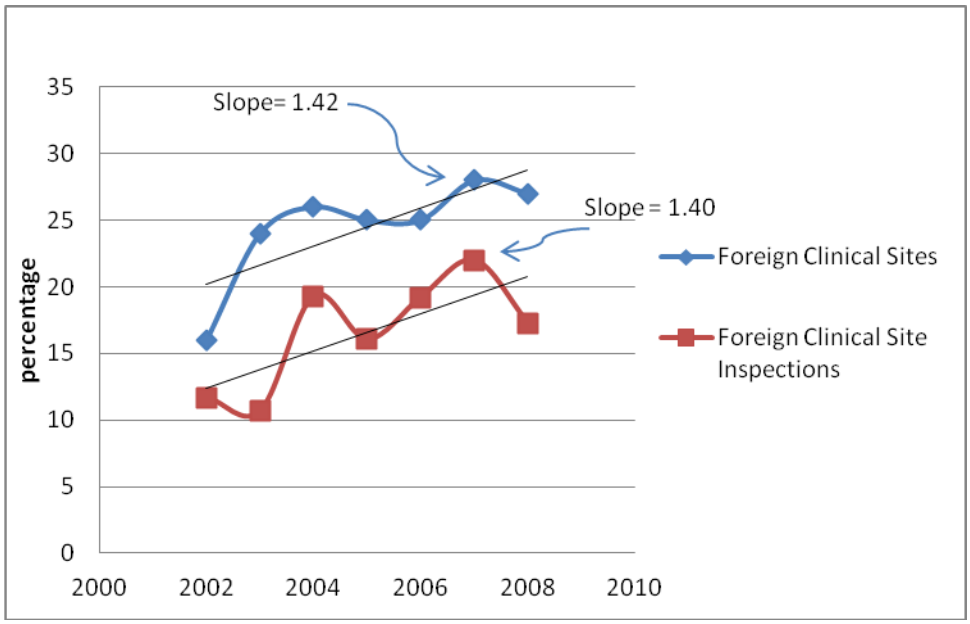

Figure 3 Regression Analysis of Foreign Clinical Sites and Foreign Clinical Site Inspections.

Slope of Percentage of Foreign Clinical Sites: 1.42
Slope of Percentage of Foreign Clinical Trail Inspections: 1.40

Figure 3 shows the slopes calculated for the percentage of foreign clinical site inspections and the percentage of foreign clinical sites through regression analysis. The slope for foreign clinical site inspections is found to be 1.40 and the slope for foreign clinical sites is 1.42. The relationship between the two slopes is shown by the R-square value, which is calculated by the regression analysis. Mainly, the R-square value is calculated to know the goodness of fit of the data. The value of the R-square between two slopes of Fig 3 found to be 0.51 and this shows

that positive relationships, this means that both the foreign clinical site inspections and foreign clinical sites are increasing. The R value of 51% denotes that 51 % of the variability occurs between the foreign clinical site inspections and foreign clinical sites.

The significance of the slopes is calculated by the P-value by ANOVA procedure. From this, the significance (F) is found to be 0.07, which is greater than 0.05 and this shows that there is a significant relationship between the increase in foreign clinical trial inspections and increase of foreign clinical sites.

Discussion

The globalization of clinical research has been increasing in the recent years, according to the Office of Inspector General of the Department of Health and Human Services (Flaherty et al., 2000). The FDA states that drug sponsors may choose multinational clinical trials and may submit their data either from domestic or foreign sites in support of an IND or for marketing applications (HHS, 2010). The importance of foreign clinical trials began in 2008 (HHS, 2010). Approximately 70% of the subjects enrolled in foreign clinical trials were from foreign countries and the clinical investigators conducting the trials under INDs doubled from 1998 to 2008 (HHS, 2010).

The results collected shows that the percentage of clinical investigators conducting clinical trials in the foreign countries have significantly increased from 1998-2008. The percentage of investigators conducting foreign clinical trials have increased from 13% in 1998 to 27% in 2008. This shows the increase in sponsors reliance on the foreign clinical trials. This is a sign that foreign clinical trial data are likely to increase in the future marketing applications. (See Figure 2.)

The data collected shows that the foreign clinical trial inspections and domestic clinical trial inspections increased from 2002 to 2009. The percentage of domestic clinical trial inspections by FDA was found to be 37% in the year 2002 and 79.3% in the year 2009. The percentage of foreign clinical trail inspections were found to be 11.7% in the year 2002 and there was an increase in the percentage of foreign clinical trail inspections to about 21.5% in the year 2009 (see Table 1).

The emergence and utilization of foreign clinical trial data have presented the FDA with significant issues regarding the inspection of clinical trials with limited availability of the

information on the foreign clinical trials. In order to maintain the integrity and safety of the human subjects, the FDA should adapt its regulations of foreign clinical trials to keep pace with the globalization. The FDA should establish more standardized methods of electronic standards of reporting and should continue to build the clinical trials registry and internal database. In this way, the FDA can able to perform analyses and can monitor to determine where the problem exists and can effectively inspect the foreign clinical trials.

The calculated slopes through regression analysis is found to be 1.40 and 1.42 for percentage of foreign clinical site inspections and the percentage of foreign clinical sites respectively. Based on the data collected, the R-square value shows that foreign clinical sites and foreign clinical site inspections are increasing and have a positive relationship. The significance value (0.07) calculated by the ANOVA procedure shows that there exists a significant relationship between the foreign clinical sites and foreign clinical site inspections (See Figure 3).

Though the FDA is moving in a same pace with globalization of clinical trials, the FDA needs to establish more ways to get the information from the non-USA institutional review boards that provides data in support of NDAs. The FDA should also make the sponsors to increase the monitoring of the sites more rigorously. As the sponsors dependency on foreign clinical trial data is increasing, all these efforts can increase the safety of human subjects and also the integrity of the data.

Conclusion

Based on the analysis of the results, it was observed that the FDA is conducting foreign clinical site inspections at the same rate as the increase of foreign clinical sites, which will still lags the rate of inspection of domestic clinical sites. Impact on the long term integrity of clinical data in US NDAs remains unknown.

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