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Assessment of the Scope and Geographic Distribution of the United States FDA's Good Clinical Practice (GCP) Inspections

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Background: The United States (US) Food and Drug Administration (FDA) conducts Good Clinical Practice (GCP) inspections to evaluate regulatory compliance, assess clinical trial conduct, and verify data integrity in support of marketing applications. To date, there has been no comprehensive assessment of the geographic distribution or extent of such inspections conducted during the marketing application review.
Methods: We conducted a retrospective analysis of FDA GCP inspection records involving clinical investigators (CIs), sponsors, and contract research organizations (CROs) associated with marketing applications submitted during fiscal years 2016 to 2018.
Results: A total of 1,275 GCP inspections were performed in support of 347 marketing applications during the study period. Inspections covered CIs (86%), sponsors (10%), and CROs (4%). On average, three CIs were inspected for each application. Most CI inspections (63%) were conducted within the US, with the remainder primarily in Europe. Of the 347 applications, 36% had sponsor inspections and 15% CRO inspections; the majority of sponsor and CRO inspections were conducted in the US (>80%). Approximately 4% of US-based and 2% of non-US-based CIs were inspected. CI inspections covered about 10% of enrolled trial participants overall (14% US vs. 8% non-US) and included review of approximately 5% of source records (8% US vs. 3% non-US).
Conclusions: While the total number of inspections and source records reviewed varied by year, the distribution of inspection types, participant coverage, and source document review percentages remained consistent. Most inspections were conducted in the US, where CI inspections also covered a higher proportion of participants and source data.

Keywords: Good clinical practice inspection; US FDA; clinical investigator; sponsor; contract research organization

Background

The US Food and Drug Administration (FDA) conducts Good Clinical Practice (GCP) inspections of clinical investigators (CIs), sponsors, and contract research organizations (CROs) to evaluate the quality and reliability of clinical trial data, compliance with applicable regulatory requirements, and the protection of participants' rights, safety, and welfare[1,2] as part of the evaluation of data submitted in support of marketing applications. When GCP inspections are deemed necessary for the review of the marketing application, the FDA review divisions in the Office of the New Drugs in the Center for Drug Evaluation and Research (CDER) make a request for inspections. These inspections are application review-based, are usually announced in advance of the inspections, and are conducted under the bioresearch monitoring program.[3] The results of the GCP inspections are integrated into the CDER's multidisciplinary review of marketing applications.

The FDA employs a risk-based approach to identify inspection sites. For CIs, selection criteria include the number of participants enrolled, the specific efficacy and safety assessment, previous inspection outcomes, and known or suspected GCP noncompliance.[4] Further considerations for selecting non-US CIs include the relative impact of non-US data on the regulatory decision; if US and non-US data show conflicting results that are significant for decision making; or if there are any data anomalies or other issues that raise data integrity concerns. The selection of sponsors and CROs for inspection considers factors such as breakthrough therapy designation, the involvement of a novel drug, the complexity and scope of the clinical development program, the vulnerability or uniqueness of the study population, and the entity's prior inspection history, including any known or suspected GCP noncompliance.

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Upon inspection completion, the findings are reviewed to assess the adequacy of trial conduct and the reliability and acceptability of the submitted clinical data. These evaluations inform FDA regulatory decisions.

This paper presents an analysis of GCP inspection data from pivotal trials submitted over a three-year period. The study evaluates the geographic distribution, scope, and frequency of GCP inspections associated with marketing applications. The aim of the study is to assess the comprehensiveness of the FDA's regulatory oversight, particularly in the context of a globally distributed research landscape.

Methods

This study utilized a retrospective, descriptive design to evaluate FDA inspection activities from fiscal years (FY) 2016 to 2018. The analysis focused on New Drug Applications (NDAs) and Biologics License Applications (BLAs) where GCP inspections were deemed necessary to support the review of the application.

Data were obtained from FDA's internal systems, including the Document Archiving, Reporting and Regulatory Tracking System (DARRTS), Compliance Management Information System (COMPLIS), Enterprise Content Management System (ECMS), and the Online Search and Retrieval System (OSARS). GCP inspection requests were identified through structured queries in DARRTS for NDA and BLA submissions within the study period.

The number of pivotal clinical trial protocols, the type and number of inspected entities (CIs, sponsors, or CROs), the geographic location (US or non-US), the number of participants enrolled under each inspected CI, the volume of source records reviewed, the number of FDA inspectors involved, and the duration of inspections were collected, reviewed, and analyzed.

Excluded from the analysis were inspection requests that were withdrawn, canceled, duplicated, or lacked sufficient data, as well as inspections conducted for bioavailability/bioequivalence studies and for-cause inspections.

Results

Between October 1, 2015, and September 30, 2018, a total of 409 GCP inspection requests related to marketing applications were identified from FDA internal databases, with 101 in FY 2016, 166 in FY 2017, and 142 in FY 2018. Of these, 62 requests were excluded from analysis for reasons outlined in **Figure 1**. The remaining 347 inspection requests were included in the final analyses.

1. Characteristics of Marketing Applications and Associated GCP Inspection Requests

Among the 347 marketing applications for which GCP inspection requests were submitted, 72% were NDAs and 28% were BLAs. Original (i.e., initial) applications comprised 71% of the total, while 29% were supplemental applications. In terms of review designation, 47% of applications received priority review status, whereas 53% underwent standard review (**Table 1**). These proportions were consistent across the three fiscal years analyzed.

Figure 1: Inspection Requests for Marketing Applications in FY 2016–2018.

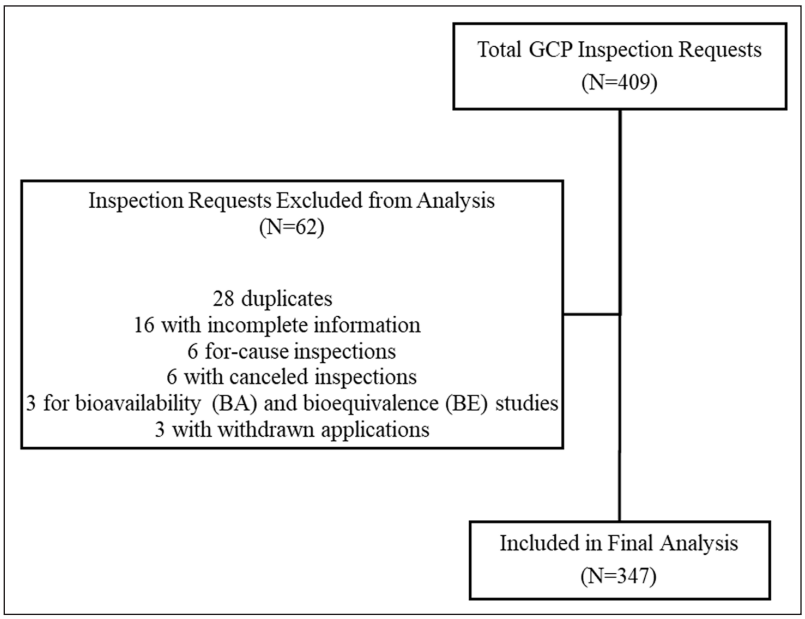


Table 1: Marketing Applications Supported by GCP Inspections in FY 2016–2018.

FY	New Drug Applications		Biologics License Applications		Review Type	
	Original	Supplement	Original	Supplement	Priority	Standard
2016	42 (50%)	16 (19%)	17 (20%)	9 (11%)	41 (49%)	43 (51%)
2017	64 (46%)	31 (22%)	30 (22%)	14 (10%)	61 (44%)	78 (56%)
2018	75 (60%)	22 (18%)	18 (15%)	9 (7%)	60 (48%)	64 (52%)

The number of individual clinical trials selected for inspection varied across applications. A single trial was requested for inspection in 55% of applications, two in 36%, and three or more in 9% of applications.

The most frequently represented therapeutic areas associated with inspection requests were oncology (28%), infectious diseases (12%), and metabolic disorders (8%).

2. Geographic Distribution of Clinical Trials and GCP Inspections

Of the clinical trials included in the 347 marketing applications, 68% were conducted in both the US and non-US countries, while 23% were conducted exclusively in the US and 9% exclusively outside of the US (**Table 2**). Most trials conducted exclusively in non-US countries were within the therapeutic areas of oncology, hematologic malignancies, and infectious diseases.

Table 2: Location of Clinical Trials Requested for Inspections in FY 2016–2018.

FY	U.S. Only	Non-U.S. Only	Both U.S. and non-U.S.
2016	14 (17%)	7 (8%)	63 (75%)
2017	34 (25%)	17 (12%)	88 (63%)
2018	32 (26%)	8 (6%)	84 (68%)

A total of 1,275 GCP inspections were conducted, with 66% (n = 841) occurring in the US and 34% (n = 434) conducted outside of the US (**Table 3**).

Among the inspections conducted outside of the US, the largest proportion took place in Europe (62%), followed by Asia (17.9%), Canada (7.4%), South America (5.9%), Africa (2.4%), Australia/New Zealand (2.2%), Central America (1.7%), and the Caribbean (0.5%). A detailed distribution by country is presented in **Figure 2**.

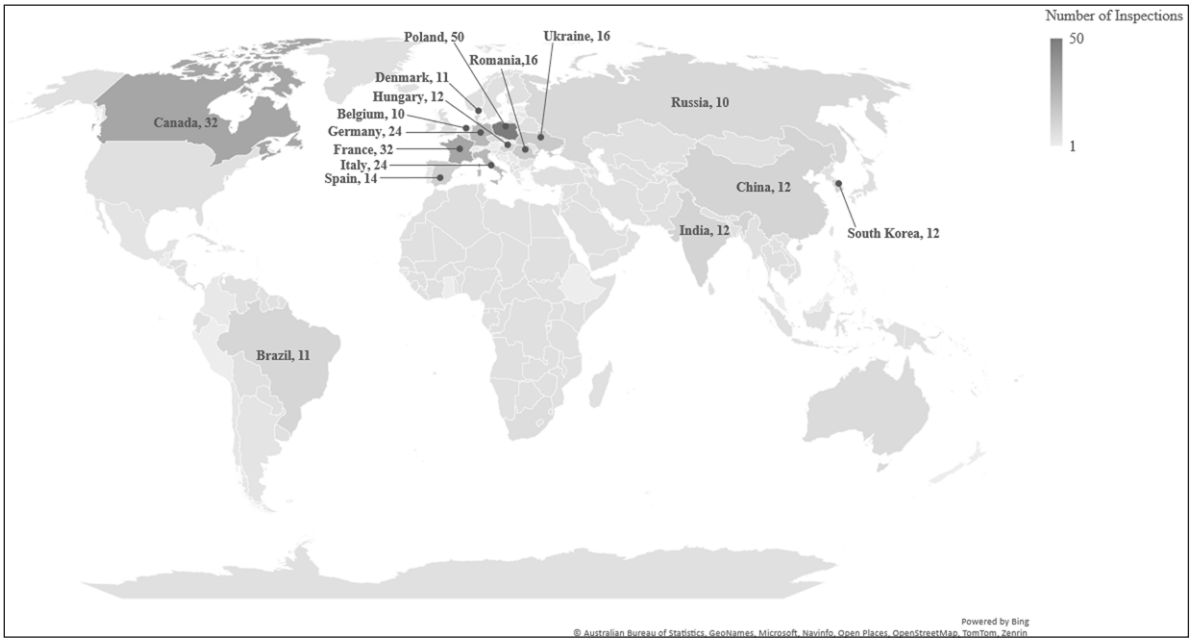
3. Overview of GCP Inspections for Application Review

A total of 1,275 GCP inspections were conducted across 347 marketing applications, yielding an average of 3.7 inspections per application. Applications that included both US and non-US clinical data underwent an average of 4 inspections, whereas those containing exclusively US or exclusively non-US data had an average of three inspections. Sponsor inspections were conducted for 36% of the applications, while 15% included inspections of CROs. On average, each application underwent three CI inspections. Of the total 1,275 GCP inspections, 86% were CI inspections, 10% were sponsor inspections, and 4% were CRO inspections.

Table 3: Establishment Type and Location for GCP Inspections in FY 2016–2018.

FY	CI		Sponsor		CRO		Total	
	U.S.	Non-U.S.	U.S.	Non-U.S.	U.S.	Non-U.S.	U.S.	Non-U.S.
2016	181 (65%)	97 (35%)	32 (91%)	3 (9%)	11 (65%)	6 (35%)	224 (68%)	106 (32%)
2017	250 (57%)	189 (43%)	37 (80%)	9 (20%)	16 (70%)	7 (30%)	303 (60%)	205 (40%)
2018	265 (69%)	118 (31%)	39 (91%)	4 (9%)	10 (91%)	1 (9%)	314 (72%)	123 (28%)

Figure 2: Distribution of Nom-U.S. GCP Inspections by Country in FY 2016–2018.



4. Inspection Coverage of Clinical Investigators and Trial Participants

A total of 45,881 CIs were involved in clinical trials submitted in support of 347 marketing applications during fiscal years 2016–2018. Of these, 1,100 CIs (2.4%) underwent FDA inspection. The inspection rate for US-based CIs (3.7%) was more than double that for non-US-based CIs (1.5%) (**Table 4**).

Across the 347 marketing applications included in this analysis, clinical trials enrolled 442,636 participants. Of these, 44,674 participants (10%) were included in the CI inspections (**Table 5**). During inspections, an FDA inspector reviewed source records to verify key clinical trial elements, including participant eligibility, efficacy outcomes, and safety data, against the data submitted by the sponsor.

In total, source records for 22,579 of the 44,674 participants (51%) were reviewed during the inspections. The proportion of reviewed source records was higher for US CI inspections than for non-US CI inspections (58% vs. 43%, respectively). Across all 347 marketing applications, participant source records reviewed during CI inspections represented 5.1% of the total enrolled population (22,579 of 442,636). A greater proportion of participant source records were reviewed during US CI inspections compared to non-US CI inspections (8.2% vs. 3.3%, respectively) (**Table 6**).

5. Inspection Duration and FDA Inspector Allocation

A total of 6,575 business days were dedicated to all inspections, averaging 5.16 business days per inspection. The average duration of US inspections was slightly longer (5.22 days) compared to non-US inspections (5.03 days). These numbers remained consistent across all three years analyzed. On average, each inspection was conducted by 1.14 FDA inspectors, with minimal variation between US (1.16) and non-US (1.09) inspections.

Discussion

This retrospective study analyzed FDA GCP inspections conducted in support of marketing application reviews between FY2016 and FY2018. While the total number of applications involving inspections varied annually, the proportions of application and submission types remained consistent across the three years. Most were NDAs and original submissions, with approximately half designated for priority review. Nearly 50% of these applications included two or more pivotal clinical trial protocols.

A majority (68%) of the pivotal trials supporting applications where inspections were deemed necessary included data from CIs in both the US and non-US. Approximately 90% of the applications contained U.S. data, while about 10% relied exclusively on non-US data.

Table 4: Number and Percentage of Clinical Investigators Inspected in FY 2016–2018.

FY	U.S.	Non-U.S.	Total
2016	181/4,407 (4.1%)	97/7,530 (1.3%)	278/11,937 (2.3%)
2017	250/6,672 (3.7%)	189/12,085 (1.6%)	439/18,757 (2.3%)
2018	265/7,534 (3.5%)	118/7,653 (1.5%)	383/15,187 (2.5%)

Table 5: Number and Percentage of Participants Covered During CI Inspections in FY 2016–2018.

FY	Number of Participants Eligible for Inspections		Number of Participants Enrolled by the Inspected CIs		Number/Percentage (%) of Participants Covered by CI Inspections		
	U.S.	Non-U.S.	U.S.	Non-U.S.	U.S.	Non-U.S.	Total
2016	36,921 (35%)	69,156 (65%)	6,929 (48%)	7,358 (52%)	6,929/36,921 (19%)	7,358/69,156 (11%)	14,287/106,077 (13%)
2017	53,733 (34%)	105,679 (66%)	6,682 (53%)	5,982 (47%)	6,682/53,733 (12%)	5,982/105,679 (6%)	12,664/159,412 (8%)
2018	70,262 (40%)	106,885 (60%)	9,260 (52%)	8,463 (48%)	9,260/70,262 (13%)	8,463/106,885 (8%)	17,723/177,147 (10%)

Table 6: Number and Percentage of Participants' Source Records Reviewed During CI Inspections in FY 2016–2018.

Fiscal Year	For the Inspected CIs			For the Inspected Studies		
	U.S.	Non-U.S.	Total	U.S.	Non-U.S.	Total
2016	3,301/6,929 (48%)	2,757/7,358 (37%)	6,058/14,287 (42%)	3,301/36,921 (8.9%)	2,757/69,156 (4.0%)	6,058/106,077 (5.7%)
2017	4,404/6,682 (66%)	3,572/5,982 (60%)	7,976/12,664 (63%)	4,404/5,3733 (8.2%)	3,572/10,5679 (3.4%)	7,976/159,412 (5.0%)
2018	5,504/9,260 (59%)	3,041/8,463 (36%)	8,545/17,723 (48%)	5,504/70,262 (7.8%)	3,041/10,6885 (2.8%)	8,545/177,147 (4.8%)

The FDA inspected over 2.4% of all CIs participating in trials associated with applications where inspections were deemed necessary for the regulatory review. Notably, the inspection rate for US CIs (3.7%) was more than double that of non-US CIs (1.5%).

CI inspections covered approximately 10% of participants enrolled in pivotal trials. Nearly two-thirds of participants were enrolled outside of the US. However, inspections covered a greater proportion of US participants. Roughly half of all participants' source records were reviewed during inspections, with a higher review rate among US participants. Language barriers and the need for interpretation likely contributed to the lower review rate of non-US records, especially given that FDA investigators typically spent about five business days per inspection regardless of location.

To support the assessment of the reliability of non-US clinical data, the FDA collaborates with international regulatory counterparts through the exchange of inspection findings.[5–7] Strengthening these global collaborations for GCP inspections enhances oversight efficiency. Leveraging such partnerships may also enable the FDA to expand its global oversight capacity while ensuring consistent quality and ethical standards in clinical research.

This descriptive study has limitations. It is based on a three-year dataset and includes only applications for which GCP review-based inspection data were available.

Conclusions

This retrospective analysis of FDA GCP inspections provides important insights into the agency's oversight of clinical trials supporting marketing applications. The majority of applications supported by pivotal trials involved both US and non-US clinical investigators. While nearly two-thirds of enrolled participants were located outside the US, inspection efforts were mostly focused on US sites and data, resulting in a higher review rate of source records for US participants. This imbalance likely reflects operational limitations, including lack of adequate resources, language barriers and fixed inspection durations.

The relatively lower inspection rate of non-US sites, despite their substantial contribution to participant enrollment, underscores the importance of continued efforts to enhance global oversight mechanisms. Ongoing collaboration with international regulatory counterparts, particularly through information sharing and joint inspection efforts, remains essential to ensure the integrity and reliability of clinical data regardless of geographic origin.

Although limited in scope and duration, this study provides valuable insight into current inspection practices and highlights opportunities to strengthen global regulatory coordination. As clinical research continues to evolve within an increasingly international landscape, targeted, risk-based oversight strategies, supported by robust international partnerships, will be critical to maintaining the quality and credibility of data submitted in support of regulatory decision-making.

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Competing Interests

The authors declare no conflicts of interest. The views expressed in this article are the personal views of the authors. They may not be understood or quoted as being made on behalf of or reflecting the agency's position with which each author is affiliated.

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