

A Comparative Review of Inspection Techniques and Regulatory Considerations between the EMA, MHRA and FDA in Clinical Trials

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Introduction

As harmonization of efforts continue for pharmaceutical companies involved in submitting data for globally-run clinical trials, the complexities of multiple submissions to local and national competent authorities make the inspection and approval process expensive, time-consuming and difficult. For example, regulatory submissions for 2009 included:

- 9,655 submissions for FDA's Office of Device evaluation
- 1,755 MHRA marketing authorizations
- 103 new applications, 22 line extensions, 19 Type II variations identified to EMA as Pivotal Trials

Whilst there are many guidance's available for industry, success in approval of multiple clinical trial applications can be improved by streamlining the process. An understanding of the similarities and differences between regulators is required in order to optimize the process.

Objective

Similarities and differences in inspection techniques used by the EMA, MHRA and FDA inspectors when a sponsor's study is selected for inspection will be identified, analysed and presented to industry to increase success in clinical trials.

Methodology

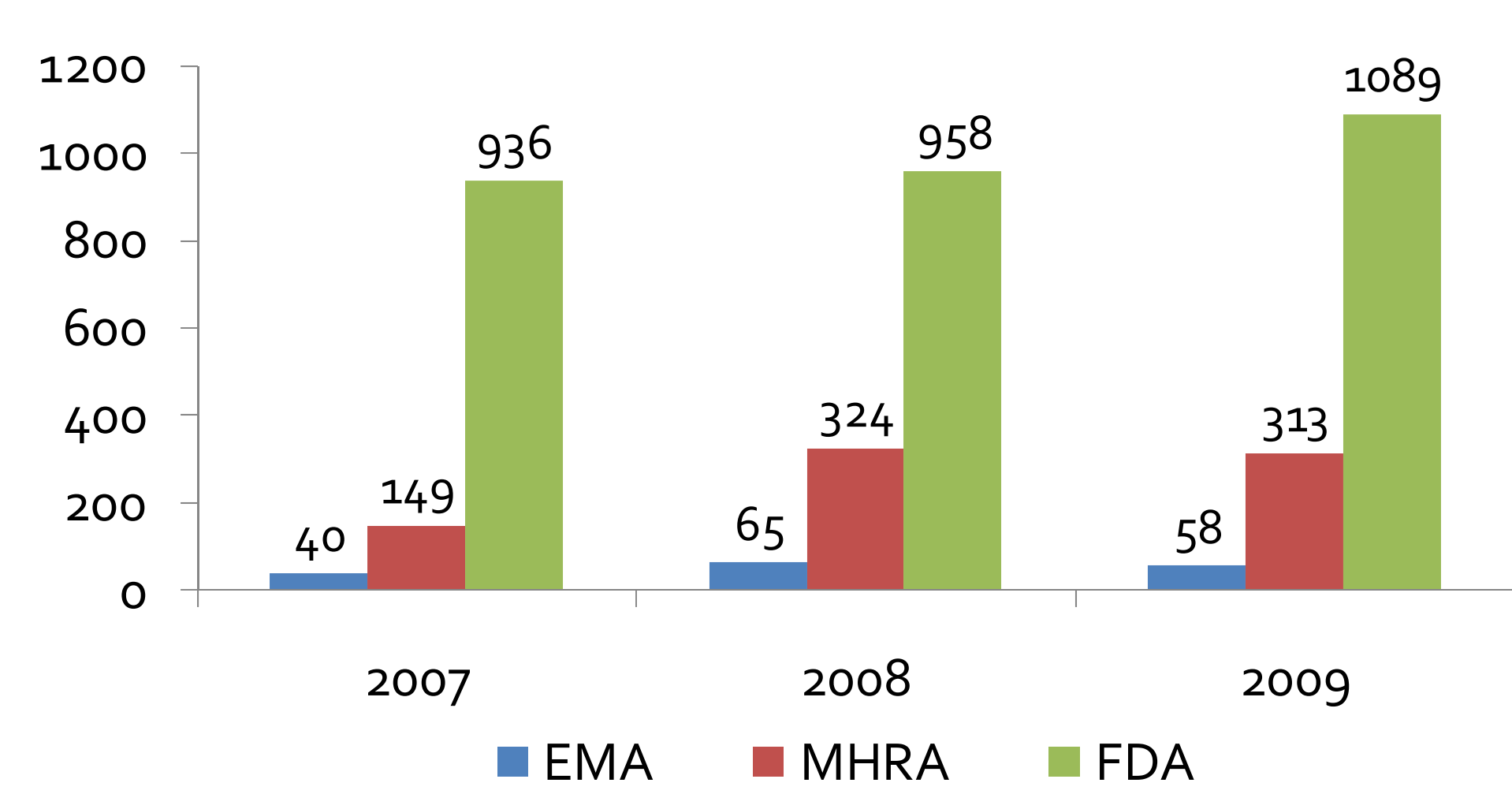
The EMA, MHRA and US FDA GCP initiatives targeted investigators, sponsors and CROs in the bioresearch industry. As the number of joint inspections continues, the ability to understand how the EMA, MHRA and FDA operate is critical to the success or failure of a submission. While there are obvious benefits to increased harmonization of regulatory bodies, it is important to understand how the regulators are similar and different in order to ensure success for data that is frequently shared globally in regulatory submissions.

Findings

Outcome data will be presented from EMA, MHRA and FDA focusing on inspectional documents requested prior to and during the inspection, the role of the inspector and similarities and differences between inspectional practices of the EMA, MHRA and FDA.

The following figure demonstrate the overall increase in the number of regulatory inspections from 2007 – 2009 for 3 regulatory bodies leading to the need for a collaborative effort to share resources for conduct of regulatory inspections.

Figure 1: Total Number of Regulatory Inspections by Regulatory Body



Data includes on-site inspections of clinical trial facilities including sponsors, monitors, clinical investigators, IRBs, and laboratories that conduct nonclinical safety studies to support applications in support of clinical research. MHRA data excludes inspection of institutional ethics committees (IECs) because it does not apply.

Some differences in the number of GCP/GLP inspections for clinical trial applications submitted resulted in lower numbers for the EMA due to a higher number of GMP inspections being conducted as compared to GCP/GLP inspections that are not accounted for in the graph. EMA conducted 145 GMP inspections in 2007, 188 in 2008 and 175 in 2009.

The following table shows that although there are differences between regulations in Europe and the US. They have similar aims and share the same principles to ensure that trials are being run according to ethical principles, patients safety, that the study is being run according to the protocol, and data integrity.

Table 1: Regulations for GCP Inspections

EMA	MHRA	FDA
<ul style="list-style-type: none"> ✓ ICH Guideline E6: Good Clinical Practice ✓ Declaration of Helsinki 1996 version (some country variations) ✓ Clinical Trials Directive 2001/20/EC ✓ GCP Directive 2005/28/EC ✓ 2001/83/EC amended by 2003/63/EC, as applicable ✓ Associated Guidance Documents ✓ Volume 10: The Rules Governing Medical Products in the European Union ✓ Local Member State laws, as applicable 	<ul style="list-style-type: none"> ✓ ICH Guideline E6: Good Clinical Practice ✓ Declaration of Helsinki 1996 version ✓ As per the EMA/EU requirements Additionally local UK laws, Statutory Instruments (SIs): <ul style="list-style-type: none"> ✓ S.I. 2008 No.941: The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 ✓ S.I 2006 No.2984: The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 ✓ S.I. 2006 No.1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 ✓ S.I 2004 No.1031: The Medicines for Human Use (Clinical Trials) Regulations 2004 	<ul style="list-style-type: none"> ✓ ICH Guideline E6: Good Clinical Practice ✓ Compliance program 7348.810: Bioresearch Monitoring for Sponsors, CROs and Monitors ✓ Compliance program 7384.811: Inspection of Clinical Investigators ✓ 21 CFR Part 11 (Electronic Records, Electronic Signature) ✓ 21 CFR Part 50 (Protection of Human Subjects) ✓ 21 CFR Part 54 (Financial Disclosure by Clinical Investigators) ✓ 21 CFR Part 56 (Institutional Review Boards) ✓ 21 CFR Part 312 (IND Applications) ✓ 21 CFR Part 812 (IDE) ✓ Local/State laws, if applicable

Legend: [Grey box] = common requirements

The following table compares the inspectional processes. While there are currently many differences, the groups are currently working on more collaborative and cooperative efforts and initiatives, e.g., inspectional pilot programs and agreements now in place.

Table 2: Comparison of Inspectional Processes between the EMA, MHRA and FDA

	EMA	MHRA	FDA
Notification process	Formal notification is made by the inspectorates of the local regions	Formal notification is made by the MHRA for routine inspections — a 'Preliminary Notification to Organization of Statutory Inspection' is issued, the organization supplies a 'Pre-Inspection Dossier, then dates are confirmed	Prior notification is not usually given unless specified by the related FDA Center
Inspection expense	Holders of the MAA for the EMA submission are required not only to cover all of the inspector's expenses but also to make all necessary travel arrangements	The MHRA charges a rate of £2,583 per day per inspector for GCP inspections (a minimum rate of 1 day is charged; trainee inspectors are not charged)	All expenses for the FDA related to the inspection are covered by the FDA
Opening meeting	No formal documentation is issued during the beginning of the inspection - instead, an opening discussion is held on the purpose of the inspection, expectations for the inspection, and verbal discussion of documents or people they need	An agenda is agreed prior to the inspection - any changes required to this by the MHRA or the site/organization are discussed at the opening meeting	FDA inspectors are required to present their credentials and issue the original signed FDA-482 form, Notice of Inspection, to the most responsible person at the firm that is being inspected
Number of inspectors	Inspectors commonly work in teams of two or three inspectors who are taken from two of the Member States	Usually 2 inspectors are assigned, but this can vary according to size of the organization or if trainee inspectors are attending	Inspectors often work alone unless the inspection is a "directed" or "for-cause" inspection which are more complex and frequently require a witness to confirm evidence collected
Request of documents	Inspectors maintain a formal tracking log of all documents requested and received	Inspectors maintain a formal tracking log of all documents requested and received	FDA makes formal verbal requests for documents, unless they are requesting copies of the firm's internal audit reports
Facility review	Inspectors typically walk through the firm's facility and ask questions to confirm and evaluate that equipment, resources/personnel, and overall facility are appropriate to the work being conducted		
Signatures	Neither the FDA nor the European inspectors are required to sign any company-requested documents		
Closeout meeting	Inspectors do not issue their list of objectionable findings at the close of the inspection, but instead discuss the findings verbally in the closeout meeting	Inspectors do not issue their list of objectionable findings at the close of the inspection, but instead discuss the findings verbally in the closeout meeting	Inspectors are required to present/issue the most responsible individual of the firm an FDA-483 in writing, if any significant objectionable conditions, relating to products and/or processes or other violations of the FD&C Act and related Acts were observed during the inspection Observations which are considered of questionable significance are required to be discussed and described in the Establishment Inspection Report (EIR), but not listed on the FDA-483
Regulatory classification of inspectional findings	Classification includes: Critical Major Minor Other	Classifications include: Critical Major Other	Classification includes: NAI—No Action Indicated VAI—Voluntary Action Indicated OAI—Official Action Indicated

Table 3 demonstrates the differences between documents requested by competent authorities following a regulatory submission. Information that is shaded in blue represents information requested prior to the audit. The EMA requests the most information prior to the audit.

Table 3: Comparison of Timing of Document Requests

	EMA	MHRA	FDA
Overview of clinical trial management and list of key researchers	During inspection	Prior to inspection**	During inspection
Overview all company facilities located within the UK involved in clinical trial activities	During inspection	Prior to inspection**	During inspection
List of computer systems and validation status	During inspection	Prior to inspection**	During inspection
List of ongoing clinical trials of IMP from previous GCP inspection or minimum of last 3 years	Prior to inspection* (list of all participating investigators; patient numbers and investigator contact information for inspected sites and written agreement from site to be inspected)	Prior to inspection**	During inspection
List of all policies /SOPs/ work instructions covering the conduct of clinical trials including adverse event reporting systems/procedures	Prior to inspection*	Prior to inspection**	During inspection
Summary information of organization's clinical trial systems including contract/agreement preparation, project management/ clinical trial monitoring, monitoring responsibility for pharmacovigilance, regulatory affairs, computer systems, Investigational Medicinal Products (IMP), data management and statistics, clinical trial reporting, and archiving, clinical facilities, equipment maintenance	During inspection	Prior to inspection**	During inspection
Monitoring visit reports	Prior to inspection* (including monitoring plan and monitor training attendance logs)	During inspection	Prior to inspection
Investigator meeting presentation, attendance log, investigator agenda	Prior to inspection*	During inspection	During inspection
Protocol and all amendments	Prior to inspection*	During inspection	Prior to inspection
Bland/sample CRFs	Prior to inspection* (for all sites inspected and in country specific language)	During inspection	Prior to inspection
Sample diary	Prior to inspection* (all versions and in country specific language)	During inspection	During inspection
Listing of all protocol deviations for investigator sites scheduled for inspection	Prior to inspection*	During inspection	Prior to inspection
Patient informed consent templates – site specific	Prior to inspection* (all languages)	During inspection	During inspection
Data listings for all subjects for all investigator sites scheduled for inspection	Prior to inspection*	During inspection	Prior to inspection
Complete study report	Prior to inspection*	During inspection	During inspection
Table of contents for Trial Master File (TMF)	Prior to inspection*	During inspection	During inspection
Instructions provided to Investigator and monitors	Prior to inspection*	During inspection	During inspection
Contact information for each site identified to be inspected	Prior to inspection*	Prior to inspection	Prior to inspection including FDA-1572s and package insert for included in NDA
Written permission from sponsor to send agency report to EU representative	Prior to inspection*	N/A	N/A
List of interpreters and directions/airport/hotel/site accommodations	Prior to inspection*	Prior to inspection	Prior to inspection

* EMA request for documents as part of the 120 day application requirement, ** GCP dossier requirements (MHRA pre-inspectional requirement for documents)

A comparison of top findings for recent Sponsor/CRO inspections between the agencies showed little overlap. The top finding for FDA was protocol/monitoring (18%) and MHRA was quality systems (14%). However, the top findings for on-site inspections for investigators did overlap as illustrated in Figure 2.

Figure 2: Comparison of Top Findings for Investigative Site Inspections

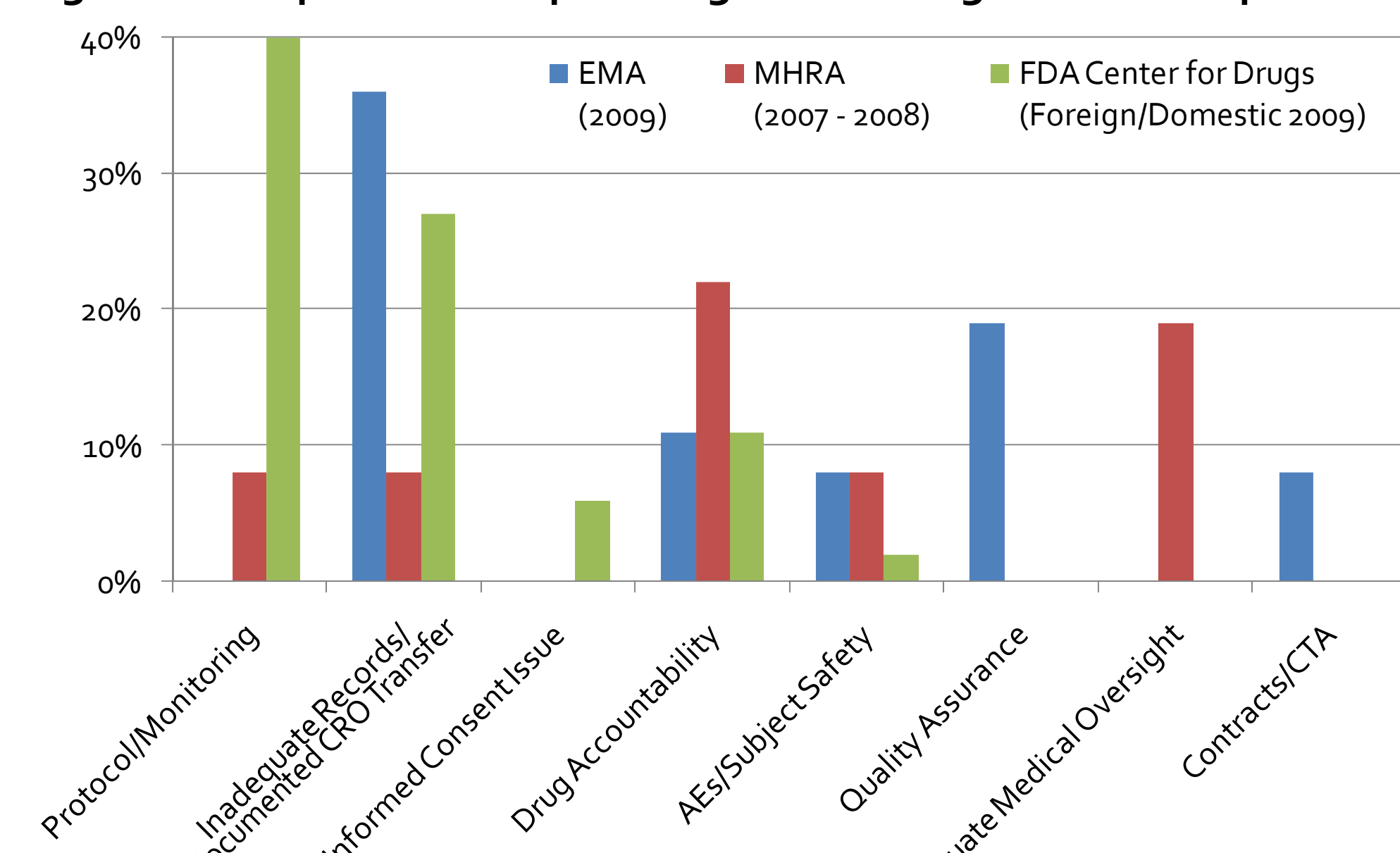


Figure 2 shows 51% of the FDA Top findings fall in one of the identified categories listed. Note that 49% of the FDA findings fall in the "No Action Indicated" column showing that the inspected firm is in compliance (not shown in the table above). Top findings for the EMA in order of significance include inadequate record/undocumented CRO transfer followed by quality assurance and drug accountability issues. Top findings for the MHRA in order of significance include the highest in drug accountability followed by inadequate medical oversight.

As shown in Table 4, both the EU/MHRA and FDA have a large arsenal of enforcement options to use to bring about compliance.

Table 4: Comparison of FDA and EU/MHRA Legal Authority Actions

EU/MHRA Legal Authority Actions	FDA Legal Authority Actions for Sponsors, Monitors, and CROs
<p>EU GCP inspections are conducted by EU Member State inspectors. The EMA does not have a role of enforcement like the FDA. Any enforcement actions are the responsibility of the individual Member States concerned and are subject to each country's local laws and regulations.</p> <p>The MHRA Enforcement & Intelligence Group (E & I) has responsibility for enforcing medicines legislation in England and does so in Scotland and Wales on behalf of the Scottish Parliament and Welsh Assembly. The strategy for enforcement is defined in the Enforcement Strategy 2010. In the UK, MHRA can issue warnings and alerts. They can also prosecute when regulations have been breached. UK courts can impose fines and prison sentences when the law has been broken. The MHRA can also withdraw any unlicensed or illegal products from the market.</p>	<ol style="list-style-type: none"> 1. Warning and Untitled Letters 2. Re-inspection 3. Termination of an exemption (IND, IDE, INAD) 4. Refusal to approve or license 5. Withdrawal of approval (PMA, NDA, NADA) 6. Determination of not substantially equivalent or rescission of a 510(k) for devices 7. Implementation of the Application Integrity Policy 8. Initiation of stock recovery 9. Seizure of test articles 10. Injunction 11. Prosecution under the FFDCa and other Federal statutes, ie, 18 USC 2, 374, 1001, and 1341 12. Referral of pertinent matters with headquarters' concurrence to other Federal, state, and local agencies for such action as that agency deems appropriate 13. Debar (or prohibit) persons who have been convicted of specific felonies or misdemeanors from participating in certain FDA-regulated activities <p><i>For Clinical Investigators, there are additional Administrative/Civil Criminal Actions that can be invoked as well as other legal sanctions under the Federal Food, Drug and Cosmetic Act (FFDCA), which includes provisions under the law to authorize the FDA to demand evidence of safety for new drugs, medical devices, and defines adulteration and misbranding of drugs and medical devices) and/or Title 18, United States Code that are not listed here.</i></p>

Conclusion

Although there are similarities in the inspection approaches implemented by European and US Regulatory Authorities, there are also important distinctions as evident in this poster. This is important as joint inspections between these groups become more common. While the joint inspection process is still in its infancy with only a handful of organizations and sites involved, the initiative aims to include the sharing of information on inspection planning, policy and outcomes, and the conduct of collaborative inspections. This is all part of the recognition that clinical trials are becoming increasingly global, with similar numbers of patients now being recruited into studies in North America, Europe and the rest of the world. The same trials are being used to support Marketing Authorization Applications (MAAs) in the EU and New Drug Applications (NDAs) or Biologics License Applications (BLAs) in the US, often as parallel assessments. Regulations in the US and Europe have similar aims to ensure that trials are being run according to ethical principles, patients are safe and well cared for, the study is run according to the protocol, and that data is recorded accurately. Inspectorates have limited resources, and inspections frequently overlap at both the site and sponsor/CRO level. These resources can be used more effectively, and joint inspections or sharing of inspection findings could be desirable for all. However, this partnership is still in its early stages and there are certain subtle differences from the beginning of the inspection to the end of the process that will need to be further explored between the way in which the agencies operate, request documents, and present findings.

Limitations of the Study

This was a retrospective review which involved all available published data, regulations and guidance's from FDA, EMA and MHRA. In some cases, data from all competent authorities was not current making a one-to-one comparison difficult.

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