AN ANALYSIS OF THE FOOD AND DRUG ADMINISTRATION AND MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY MUTUAL RECOGNITION AGREEMENT

By

Samuel Francis Egas

(Under the Direction of Michael Bartlett)

ABSTRACT

In 2017 the Food and Drug Administration (FDA) of the United States and the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom signed a mutual recognition agreement (MRA). This report summarizes the entirety of the FDA-MHRA MRA, details the inspection process of both regulatory agencies, and analyzes the foundation of the MRA that is regulatory harmonization. Furthermore, the report analyzes potential effects of the recently signed FDA-MHRA MRA by comparing good manufacturing practices (GMP) enforcement action data. Although the report finds no major effects from the GMP enforcement action data, due to insufficient data and the COVID-19 pandemic, the report lays a framework for future GMP enforcement action data analysis.

INDEX WORDS: US Food and Drug Administration, UK Medicines and Healthcare Products Regulatory Agency, Mutual Recognition Agreement, GMP Enforcement Action Data, Regulatory Harmonization

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SAMUEL FRANCIS EGAS

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SAMUEL FRANCIS EGAS

Major Professor: Michael Bartlett
Committee: Gurvinder Singh Rekhi
Randall Tackett

Electronic Version Approved:

Ron Walcott
Dean of the Graduate School
The University of Georgia
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CHAPTER 1

BACKGROUND OF THE MUTUAL RECOGNITION AGREEMENT

"Mutual Recognition Agreements (MRAs) between the FDA and foreign regulatory authorities allow for drug inspectors to rely upon information from drug inspections conducted within each other's borders."[1] The ability to recognize drug inspections conducted by foreign regulatory authorities is allowed under the Food and Drug Administration Safety and Innovation Act (enacted in 2012) as long as the "FDA determines those authorities are capable of conducting inspections that meet U.S. requirements."[1] The FDA and Medicines and Healthcare products Regulatory Agency (MHRA) state MRAs have the potential to "yield greater efficiencies for U.S. and foreign regulatory systems by avoiding duplication of inspections"[1] which will "enable reallocation of resources towards inspection of drug manufacturing facilities with potentially higher public health risks around the world"[1]. The FDA has collaborated with the EU (European Union) since May 2014 regarding how each regulator inspects drug manufacturers as well as the assessment of the risk and benefit that comes with mutual recognition of drug inspections.[1] The MRA between the FDA and the MHRA was officially recognized on November 1st, 2017.[1] The FDA has continued its "collaboration with the United Kingdom since it exited the EU as of January 1st, 2021."[1] The United States and European Union signed an MRA in 1998, which included a Pharmaceutical Annex providing for recognition of each other's GMP inspections, but it was never fully implemented.[4] The agreement has been "fully operational for human medicines as of July 11th, 2019"[5]. This also marked the end of the transition phase.[5]

The Mutual Recognition Agreement between the United States and the United Kingdom has a much larger scope than simply good manufacturing practice (GMP) of pharmaceuticals. The MRA includes the "conditions under which each country will accept conformity assessment results from the other".[2] The UK-USA MRA covers: electromagnetic compatibility (EMC), telecommunication equipment, and GMP of pharmaceuticals.[2] The following discussion is a summary of the crucial articles about GMP enforcement actions. The first article concerns definitions. Below is Table 1 with the full list of definitions.[3]

Table 1: Full List of Definitions in MRA[3]

Term	Definition
Capable Authority	An authority that the Food and Drug Administration (FDA) FDA has determined is capable according to the criteria and procedures specified in Appendix 4 and Appendix 1. For greater certainty, a finding that a regulatory authority is "capable" does not require that the authority maintain procedures for conducting inspections and overseeing manufacturing facilities that are identical to FDA's procedures
Equivalent Authority	An authority in respect of which the EU has made a positive equivalence determination according to the criteria and procedures specified in Appendix 4 and Appendix 1.
Equivalence	The regulatory system under which an authority operates is sufficiently comparable to assure that the process of inspection and the ensuing official GMP documents will provide adequate information to determine whether respective statutory and regulatory requirements of the authorities have been fulfilled. For greater certainty, "equivalence" does not require that the respective regulatory systems have identical procedures.
Enforcement	An action taken by an authority to protect the public from products of suspect quality, safety, and efficacy or to assure that products are manufactured in compliance with appropriate laws, regulations, standards, and commitments made as part of the approval to market a product.
Good Manufacturing Practices (GMPs)	Systems that assure proper design, monitoring, and control of manufacturing processes and facilities, the adherence to which assures the identity, strength, quality, and purity of pharmaceuticals. GMPs include strong quality management systems, obtaining appropriate quality raw materials (including starting materials) and packaging materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.
Inspections	An on-site evaluation of a manufacturing facility to determine whether such manufacturing facility is operating in compliance with Good Manufacturing Practices and/or commitments made as part of the approval to market a product.
Inspection Report	A report written by an investigator or inspector of an authority listed in Appendix 2 concerning an inspection of a manufacturing facility that the investigator or inspector conducted that describes the purpose and scope of an inspection and includes written observations and findings bearing on the manufacturing facilities conformance to applicable GMP requirements set out in the laws, regulations and administrative procedures listed in Appendix 1 and any commitments made as part of the approval to market a product.

Official GMPs Document	A document issued by an authority is listed in Appendix 2 following an inspection of a manufacturing facility. Examples of official GMPs documents include inspection reports, certificates issued by an authority attesting to the compliance of a manufacturing facility with GMPs, GMPs non-compliance statement issued by authorities of the EU, and notice of observations, untitled letters, warning letters, and import alerts issued by the FDA.
Pharmaceuticals	Drugs and medicinal products as defined in the laws and regulations listed in Appendix 1.
Post-approval inspections	GMP surveillance inspections during the marketing of products.
Pre-approval inspections	Pharmaceutical inspections of manufacturing facilities are carried out in the territory of a Party as part of the review of an application before marketing approval is granted.
Regulatory System	The body of legal requirements for Good Manufacturing Practices, inspections, and enforcements that ensure the public health protection and legal authority to assure adherence to these requirements.

The next two articles, Articles 2 and 3, address the purpose and scope of the MRA, respectively. The purpose of the MRA is to allow the FDA and MHRA to "use inspection reports and other related information obtained during current GMP surveillance inspections, whether conducted by the MHRA or by the FDA, to determine whether a facility is manufacturing high-quality drug".[4] This allows for each agency to "leverage and reallocate its inspection resources"[3] by avoiding duplicate inspections. This can "improve oversight of manufacturing facilities and better address quality risk and prevent adverse health consequences."[3] The scope of this agreement applies to GMP surveillance inspections, pre- and post-approval inspections, as well as, "pharmaceutical inspections of manufacturing facilities carried out outside the territory of either agency". [3] Within article 3, the laws, regulations, and administrative provisions govern GMP inspection requirements are stated.[3] Additionally, it identifies the "authorities responsible for the oversight of these facilities".[3]

Article 4 describes the products covered within the agreement. The MRA applies to "marketed finished pharmaceuticals for human or animal use, intermediates, in-process

materials, certain marketed biological products for human use, and active pharmaceutical ingredients (APIs)".[3] The full detailed list of products covered is within Appendix 3. "Human blood, human plasma, human tissues/organs, and veterinary immunologicals are excluded from the scope".[3]

Article 5 and 6 are concerned with the idea of recognition of authorities and recognition of inspections, respectively. Recognition of authority means the United States recognizes the MHRA as a capable authority and the United Kingdom recognizes the FDA as an equivalent authority.[3] The difference between a "capable authority" and an "equivalent authority" is found in Table 1. Recognition of inspections implies each agency recognizes "pharmaceutical inspections and accepts official GMP documents issued by the recognized authority of the other country for manufacturing facilities located in the territory of the issuing authority".[3] Article 6 explains that accepting an "official GMP document means relying on the factual findings in the document".[3] There are also situations where each agency may not accept the official GMP documents. The process for dealing with this is explained in Article 6. Another key detail in this article is that each country can "accept official GMP documents issued by a recognized authority of other countries for manufacturing facilities located outside the territory of the issuing authority".[3] This exponentially increases the reallocation of resources since most pharmaceutical manufacturing facilities are located outside of the United States and the United Kingdom.

Article 7, Batch Testing, alleviates the strained resources of both agencies. This article states that qualified persons "will be relieved of the responsibility of carrying out the controls provided that the controls have been carried out in the United States, the product was manufactured in the United States, and that each batch/lot was accompanied by a batch certificate".[3] Article 8 describes transmission of official GMPs documents and that those

documents must be submitted "within 30 calendar days from the date of the request".[2] Based on the GMP documents, each agency has the right to request a new inspection.

Article 9 "Requests for Pre-approval, Post-approval, and GMP Surveillance Inspections"[3] is critical to the foundation of this agreement. This article defines out the process for requesting inspections. Each request must have a reason and a precise issue that must be addressed in the inspection, as well as, a "timeline for completing the inspection and transmitting the official GMP documents".[3] Each authority has "15 calendar days of receipt of the request"[3] to confirm whether it will inspect per the requested timeline.[3] Interestingly, if the recognized authority refuses to "conduct the inspection, the requesting authority has the right to conduct its own inspection of the manufacturing facility"[3]. I will only be focusing on the published GMP surveillance inspection data from the MHRA and FDA.

Article 10 "Maintenance" allows for each country to "maintain ongoing activities to monitor whether recognized authorities in its territory are maintaining the criteria for recognition".[3] Article 11 "Suspension of a Recognized Authority" states that "each party has the right to suspend recognition of a recognized authority"[3]. It also explains the process, the involvement of the Joint Sectoral Committee, the timeline, and how the reasons for suspension must be in "sufficient detail to allow the authority of the other party to understand corrective measures that must be taken to lift the suspension".[3]

Article 12 "Role and Composition of the Joint Sectoral Committee" is also critical to be able to understand the full background of the MRA. This Committee is "set up to monitor the activities performed under this Sectoral Annex and is co-chaired by a representative from the FDA and a representative from the MHRA".[3] Each decision made by the Joint Sectoral Committee will be by unanimous consent and all rules/procedures will be made by the

Committee. The article describes in detail the four main functions of the committee. The Committee is tasked with developing and staying current with the list of recognized authorities (including limitations), providing a forum to discuss issues, deciding the status on the "inclusion of the products covered in the agreement, and lastly adopting when necessary, appropriate complementary technical and administrative arrangements for the effective implementation of this Sectoral Annex".[3]

Article 13 "Regulatory cooperation" states that both "parties shall inform and consult one another on proposals to introduce new controls or to change existing technical regulations or significant changes to pharmaceutical inspection procedures".[3] Article 14 "Exchange of Information" describes the appropriate arrangements needed concerning any "confirmed problem reports, corrective actions, recalls, rejected import consignments, and other regulatory and enforcement problems for products"[3] within the scope of this agreement. Article 15 "Alert System" is concerned with the ability for each authority to be "made aware proactively and with appropriate speed in cases of quality defect, recalls, counterfeit, falsified products, potential serious shortages, and non-compliance with GMPs."[3] Article 16 "Safeguard Clause" is concerned with each party having the right to "fulfill its legal responsibilities by taking actions necessary to ensure the protection of human and animal health at the level of protection it deems appropriate."[3] This means each party has the "right to conduct its own inspection of a manufacturing facility in the territory of the other party".[3]

Article 17 "Transitory Provisions" is the final article in the Sectoral Annex for Pharmaceutical GMPs. It is worth noting again that the amended MRA was written in 2017. The first point in this article is that "within four months following the entry into force of the agreement, the Joint Sectoral Committee will consider whether to include veterinary products

within the scope of the agreement".[3] In March of 2020, both authorities agreed veterinary products would be covered under the MRA. The next point in the article is concerned with "whether to include vaccines for human use and plasma derived pharmaceuticals within the scope of the MRA."[3] No decision had been made yet with the deadline for this decision being July 15, 2022. The third point in this article is related to pre- and post-approval inspections. It states that "no later than four months following the entry into force of this agreement, the Joint Sectoral Committee shall review experience gained to decide if it should be reviewed."[3] As of July 2019, both the FDA and EU have been actively engaged in evaluating how best to implement the US-EU MRA for consideration of pre-approval inspections.[4]

Following the 17 articles of the MRA, there are 4 appendixes. Appendix one lists the "applicable laws, regulations, and administrative provisions"[3] for the United States and the United Kingdom. For the United States, it refers to the "Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and 21 CFR Parts 210, 211, and 600 (subpart B and C)."[3] The United Kingdom refers to the "Human Medicines Regulations 2012, the Veterinary Medicines Regulations 2013, and the Medicines for Human Use (Clinical Trials) Regulations 2004."[3] The following appendix simply lists the authorities which are the FDA, MHRA, and the Veterinary Medicines Directorate. Appendix three contains the entire list of products covered by the sectoral annex. The following list is copied directly from the MRA.

"1. Marketed finished pharmaceuticals for human use in various pharmaceutical dosage forms such as tablets, capsules, ointments, and injectables, including:

(a) Medical gases

(b) Radiopharmaceuticals or radioactive biological products

(c) Herbal (botanical) products*

(d) Homeopathic products

2. Marketed biological products

(a) Vaccines for human use**

(b) Plasma derived pharmaceuticals**

(c) Therapeutic biotechnology-derived biological products

(d) Allergenic products

3. In process materials (for the United States as defined under U.S. law) and intermediates (for the European Union as defined in EU legislation)

4. Active pharmaceutical ingredients or bulk drug substance

5. Investigational products (clinical trial material)***

6. Veterinary products**

(a) veterinary pharmaceuticals, including prescription and non-prescription drugs, with the exclusion of veterinary immunologicals

(b) pre-mixes for the preparation of veterinary medicated feeds (EU), Type A medicated articles for the preparation of veterinary medicated feeds (US)

* Included to the extent that they are regulated as drugs by the FDA and MHRA

** Only included within the product coverage to the extent the Joint Sectoral Committee decides to include them

*** The FDA does not routinely conduct GMP inspections for investigational medicinal products. Inspection information on these products will be provided to the extent that they are available, and resources allow. These products are only included within the product coverage to the extent the Joint Sectoral Committee decides to include them."[3]

Appendix four provides the criteria for assessments. The first part describes the criteria needed to determine whether to recognize an authority. Since the FDA and MHRA are the respected authorities and this is not expected to be changed, I will not go through the full list of

criteria. The second part details the procedures for assessment of the MHRA by the FDA and then followed by an assessment of the FDA by the MHRA. The assessment of the UK is initiated when the UK submits a capability assessment package containing several different materials. This happens before the FDA initiates its assessment. The FDA may require further information, however, it also can waive certain information and request alternate material. These decisions are made on a case-by-case basis. The following are the materials contained in the capability assessment package.

1. "A finalized Pharmaceutical Inspection Convention Scheme (PIC/S) audit report (includes a full report of an observed inspection, any associated corrective measures, and other documents identified as essential for the assessment)*
2. A completed conflicts of interest questionnaire established by the FDA
3. A total of four inspection reports including the report from the inspections observed during the PIC/S audit*
4. Standard operating procedures (SOPs) or descriptions on how the MHRA finalizes inspection reports
5. SOPs related to training and inspector qualification (includes the training files for inspectors who conducted the inspections in the reports provided to the FDA)
6. The most recent inventory of manufacturing facilities within its territory and under the authority of the MHRA"[3]

**PIC/S related material is discussed in Chapter 3*

The MHRA carries out its assessment of the FDA in a different way. It is based on the "performance of an audit in the framework of the PIC/S and audits performed in the context of

the Human Medicines Regulation 2012."[3] Additionally, there is an "assessment of the equivalence of legislative and regulatory GMPs requirements."[3]

The MRA concludes with a section on the "reassessment of an authority" and a section on "maintaining recognition". The first section simply means that if the FDA or MHRA issues a "suspension or negative determination of the other agency, it may reassess the authority."[3] Lastly, the two parties are required to continue to meet the criteria set out in this agreement and that they must be audited every five to six years.[3]

CHAPTER 2

THE INSPECTION PROCESS

The FDA and MHRA both have the same goal of protecting public health. However, the two agencies may approach this goal quite differently. One transparent difference in how they achieve this is the way the two agencies perform their inspections. Looking into the inspection process of both agencies provided insight into the difficulties of executing an MRA. It also allows for a different approach in analyzing GMP enforcement data between the two agencies. Since the MRA has focused heavily on surveillance/routine inspections and less on pre-approval inspections, I will be predominately reviewing the surveillance inspection process of both agencies.

FDA surveillance inspections have changed a great deal during the 21st century. It is important to look at how the FDA chooses which sites get inspected. Prior to 2012, the FDA was "required to inspect domestic establishments that market drugs in the United States every two years with no comparable requirement for foreign establishments."[7] However, in 2012 "Risk-Based framework for prioritizing sites for GMP inspections"[7] was established and eliminated the two-year requirement. Three factors influence site risk potential. They are (1) the type of products manufactured at the site, (2) the types of processes utilized at the site, and (3) the type of facility.[6] There are two main goals the FDA has with this risk-based approach. The first goal is to "ensure that the FDA's resources are used effectively and efficiently to address the most significant public health risks."[6] Secondly, the FDA aims to put risk in the context of pharmaceutical quality.[6] That means knowing the "potential harm associated with the loss of

pharmaceutical quality or the probability/severity that a drug will fail to meet the needs/expectations of the patients and their surrogates."[6] Those needs can be seen in the clinical performance and availability of the drug. The FDA has created a "Risk Ranking Model" to determine this. This includes analyzing the intrinsic properties of products to see what products potentially have more adverse public health impacts than others.[6] For example, products with a higher risk could be sterile products, prescription products, and non-medical gases. Another component of this model is the analysis of recall data to "identify products or dosage forms that are associated with frequent and/or serious recalls".[6] It is known that the following facilities routinely get inspected: "dosage formulation, API, biotech, medical gas processors and transfillers, contract packagers/labelers, contract sterilizers, contract laboratories, and 'export only' involved facilities."[6]

The FDA's focus of surveillance inspections is on "system-wide controls that ensure the manufacturing process produces quality drugs"[43] intending to ensure "establishments consistently manufacture drug products of acceptable quality and minimize consumers' exposure to adulterated drug products."[7] The FDA has identified four objectives of surveillance inspections.[7] They first are to "determine whether inspected firms are operating in compliance with applicable cGMP (current Good Manufacturing Practices) requirements, and if not, to provide the evidence for actions to prevent adulterated products from entering the market."[7]Additionally, as appropriate, to "remove adulterated products from the market, and to take action against persons responsible."[7] The second objective is to "provide an assessment of firms' conformance to cGMP requirements for agency decisions."[7] The next objective is to "provide input to firms during inspections to improve their compliance with regulations."[7]

Lastly, the FDA wants to “understand current practices in drug manufacturing to update cGMP requirements, regulatory policy, and guidance documents.”[7]

The FDA has organized inspections into sets of operations and related activities, known as systems.[7] The focus on systems increases the efficiency of conducting inspections. The FDA defines inspections as an “audit covering two or more systems, with mandatory coverage of the quality system.”[7] There is a clear emphasis on the quality system throughout inspections. This emphasis will also be seen later in Chapter 4, GMP enforcement action data. Interestingly, this scheme of systems was taken “directly from the subchapter structure of the 21 CFR 211 cGMP regulations.”[7] It is worth noting that organization, personnel, and records are included within the context of each system. The following are the “six systems for auditing the manufacture of drugs and drug products: quality system, facilities and equipment system, materials system, production system, packaging and labeling system, and laboratory control system.”[7]

There are two types of FDA surveillance inspections. The first is a "Full Inspection Option". This is an inspection meant to “provide a broad and in-depth evaluation of a firm's conformance with cGMP requirements.”[7] This normally includes an inspection audit of at least four systems, one of which must be the quality system.[7] The second type of FDA surveillance inspection is the "Abbreviated Inspection Option". This is meant to “provide an efficient updated evaluation of a firm's conformance with cGMP requirements.”[7] An abbreviated inspection can change to a full inspection if there are “objectionable conditions found in one or more systems.”[7] This inspection usually includes an audit of at least two of the systems that are rotated in successive abbreviated inspections.[7] The following table compares and contrasts the two surveillance inspection types.

Table 2: Comparison between Full Inspections and Abbreviated Inspections[8]

Full Inspection option	Abbreviated Inspection Option
• Initial Inspection • History of noncompliance • Significant changes (new technologies, equipment, facilities • Follow-up to a warning letter • Revert to an abbreviated option with district concurrence	• When not using the full inspection option • Adequate for routine coverage • No significant recalls or product defects or field alert incidents • Little shift in manufacturing profiles within the previous two years • Rotate systems with the abbreviated option, districts will monitor

Inspection planning is an additional key aspect of surveillance inspections. This happens before the scheduling of surveillance inspections. "The Office of Quality Surveillance (OQS) in the Office of Pharmaceutical Quality (OPQ)/CDER prepares an up-to-date site dossier."[7] This includes "quality information on facility inspection history, recalls, shortages, customer complaints, foreign regulator inspection outcomes, information on submitted Field Alert Reports or (FARs) or Biological Product Defect Reports (BPDRs), submitted quality metrics data if available, and a listing of all products manufactured at the site."[7] It is important to know that when a system is inspected, "the inspection of that system may be considered applicable to all products which use the system."[7] "Selection of products is made so that coverage is representative of the firm's overall abilities in manufacturing within cGMP requirements."[7] Inspectors typically prepare for an inspection by "reviewing application or Drug Master File (DMF), guidance documents, cGMPs, the FFDCA (Federal Food Drug, and Cosmetic Act), FDA compliance programs, and the Investigations Operations Manual (IOM)."[8] The IOM is the

"primary source of information regarding Agency administrative and general procedural rules for FDA employees who perform field investigational activities."[8] This helps assure quality, consistency, and efficiency in the field of operations.[8]

An FDA surveillance inspection begins when the Notice of Inspection (also known as the FDA-482 form) is issued.[8] All FDA team members must sign the document and the original is given to the firm with an additional copy included in the Establishment Inspection Report (EIR).[8] The FDA inspectors display their credentials followed by the lead investigator stating the purpose of the inspection and providing a general agenda.[8] Typically, a tour of the facility is given next, followed by a "daily wrap up meeting" concluding the beginning of the inspection. In the "FDA Compliance Program Chapter 56: Drug Quality Assurance Program 7357.002" document, the extensive and detailed system inspection coverage can be found for each of the six systems. This contains the list of items the firm should have "written and approved procedures and documentation for"[7]. The inspectors verify through observation whenever possible.[7] The inspectors record regulatory notes consisting of a "contemporaneous, sequential record of daily investigatory efforts, observations relevant to violations, positive findings, and corrective actions."[8] They should be "accurate, objective, factual, and free of personal feelings or conclusions."[8]

The inspection ends with a "formal close out". This can include sample collections, affidavits (for domestic inspections), and issuance of FDA 483/inspectional observations.[8] The inspection is classified into one of three categories: No Action Indicated (NAI), Voluntary Action Indicated (VAI), and Official Action Indicated (OAI).[8] The firm will be given a copy of the FDA inspection report. Only pre-approval investigations are provided with recommendations following the end of the inspection, post-approvals are not provided recommendations. The FDA

investigators will leave the facility and write the EIR. This must be done in a "timely manner and incorporates all inspectional findings from each member."[8] The investigators also communicate with District personnel (Investigations Branch and Compliance Branch) and with the laboratory to prepare sample collection reports.[8] Investigators additionally submit any recommendations the District may have.[8]

The MHRA differs in its way of handling GMP inspections. The MHRA has three types of inspections: (1) requested inspections, (2) triggered inspections, and (3) routine inspections. Routine inspections are comparable to the previously discussed FDA surveillance inspections. The MHRA does not have an equivalent document to the FDA Compliance Program, 7356.002 which details the surveillance inspection. Information on MHRA routine inspections that is similar to the level of detail found in the FDA compliance program is not available. However, the agency does have some more general information on the process on its website.

Some aspects of MHRA routine inspections are very similar to the FDA surveillance inspections, a clear example is the "risk-based compliance programme" of the MHRA. This is "the system in which every manufacturer and wholesaler has a risk rating or score that prioritizes inspections for those with the highest ratings or scores."[9] The GMP rating is based on three main areas: "(1) the firm's compliance report, (2) internal information about previous inspection history, and (3) organizational changes."[9] The firm will be notified about the inspection in advance, however under the "short-notice inspection programme" the MHRA may send little or no notification.[9] Interestingly, the firm is unable to appeal its risk rating. The firm will be given a "full copy of the reasons for the risk score rating after the inspection."[9] If there is an increase in risk, it will be "peer-reviewed by the GMP operations manager, a member of the compliance management team (CMT), and a GMP expert inspector before being finalized."[9]

The MHRA states that the inspector team will “interview relevant personnel, review documents, and conduct site visits.”[9] Facilities included in site visits are those “producing, purchasing, and distributing medicines.”[9] This encompasses “manufacturing areas, quality control (QC) laboratories, stock and stock management, storage areas, temperature monitoring, return areas, purchasing and sales functions, and transportation arrangements.”[9] The inspectors have the right to “ask for additional documentation and/or samples for testing throughout the inspection process.”[9] They may change the “focus of the inspection if they suspect serious non-compliance.”[9] The inspection ends with a closing meeting where the team provides feedback and discusses any deficiencies that may have been discovered.[9] In this closing meeting, there will be an agreement on the timeline for any potential corrective actions.[9]

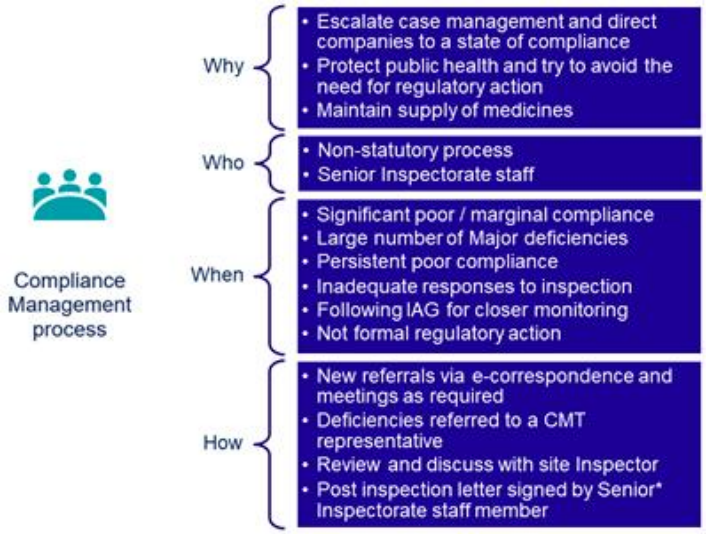
The MHRA and EMA (European Medicines Agency) grade deficiencies found during inspections at 3 levels. The most serious deficiency is a "critical deficiency". This is one that has “produced or significantly risks producing a product that is harmful to humans or veterinary patients or which could result in a harmful residue in a food-producing animal.”[9] The next level of deficiency is a "major deficiency". This is described as a “non-critical deficiency that has or may produce a product that doesn't comply with its marketing authorization.”[9] It indicates a “major deviation from GMP or GDP (Good Distribution Practices) or the terms of the manufacturer license or wholesale license.”[9] Additionally, it indicates a “failure to carry out satisfactory batch release procedures.”[9] Lastly, it can be a combination of several "other deficiencies" which on “their own may not be major but together may represent a major deficiency.”[9] The third and least severe type was just mentioned and is known as "other

deficiencies". The MHRA describes these as a deficiency that “cannot be classified as either critical or major or there is not enough information to classify it as critical or major but indicates a departure from GMP and GDP.”[9]

Once the inspection has concluded, the agency sends a “post inspection letter confirming any deficiencies found.”[9] The firm is responsible for responding to the post inspection letter with proposed corrective actions and dates for when actions will be completed. If the inspection team finds the response acceptable, a GMP certificate is issued with the inspection report. If the response is unacceptable, it may lead to a “compliance escalation if further requests for information are unsatisfactory.”[9] Additionally, if there are any changes to the site, the firm is required to complete an interim assessment.

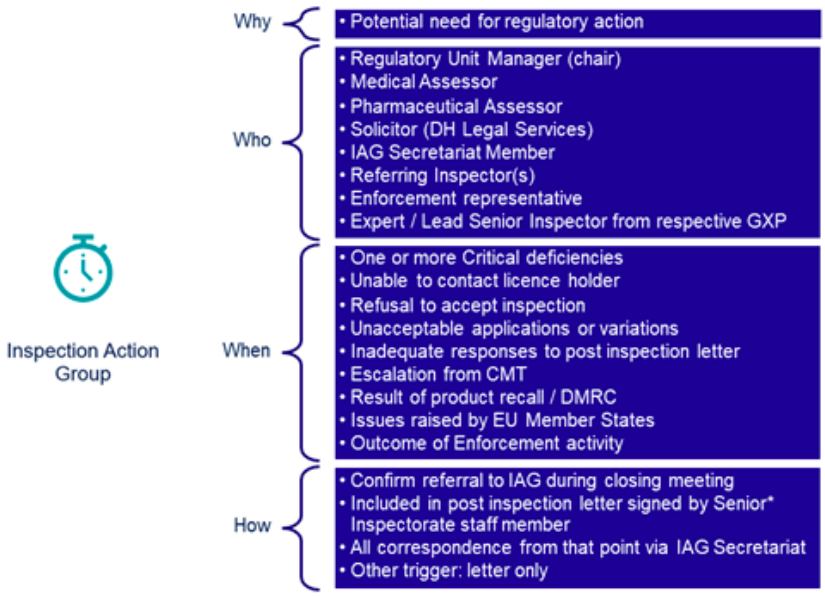
The MHRA has a compliance escalation process that is utilized for situations of poor compliance but not reaching the threshold for regulatory action. The purpose of this process is to “support companies to achieve compliance before regulatory action becomes necessary.”[9] The MHRA briefly describes the process on their website. It describes it as “making recommendations on close monitoring of compliance improvement work through inspections.”[9] It includes “meetings and correspondence with company senior management where they clearly outline the consequences of continued non-compliance.”[9] The following figure is an overview of the compliance management process.

Figure 1: Overview of MHRA Compliance Management Process[10]



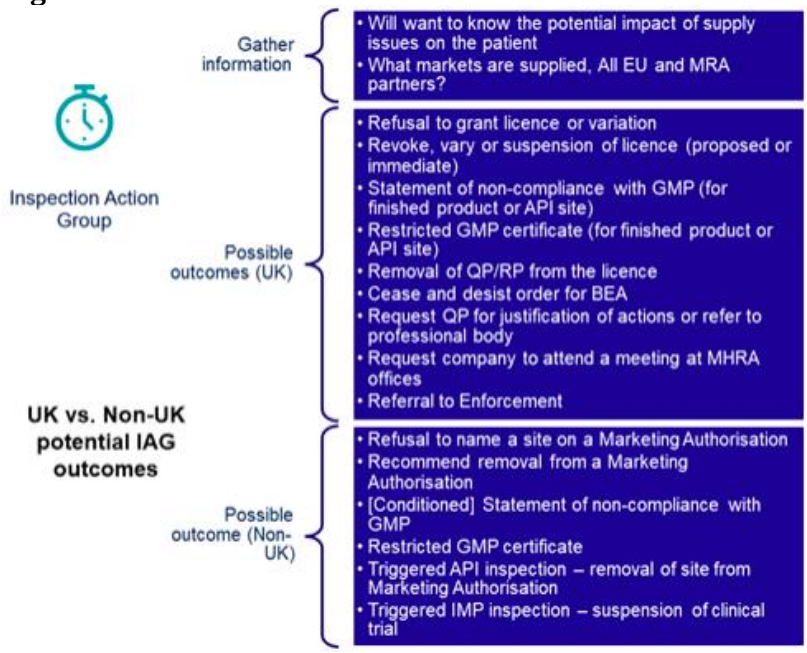
A separate process for situations in need of potential regulatory action involves the Inspection Action Group (IAG). This team can "refuse or suspend a license, increase inspection visits, or request a meeting with license holders."[9] It is made up of a "cross-functional team that encompasses expertise from across the agency and external bodies where needed."[9] Sites are typically referred to this group when they have one or more critical deficiencies.[10] It can also occur if the firm refuses to "accept an inspection or has poor responses to quality issues."[10] The following figure summarizes the IAG process.

Figure 2: Overview of MHRA IAG Process[10]



Firms will typically be notified that a referral to IAG is likely at the closing meeting. The group "normally meets every two weeks, however, it can hold emergency meetings for urgent referrals."[10] The following figure summarizes the possible outcomes for UK firms and Non-UK firms.

Figure 3: UK vs. Non-UK Potential IAG Outcomes[10]



CHAPTER 3

REGULATORY HARMONIZATION

A major underlying theme behind an MRA is the idea of regulatory harmonization. This goal of regulatory harmonization is crucial due to the increased globalization in the pharmaceutical industry. The FDA describes regulatory harmonization as the "process where regulatory authorities align technical requirements for the development and marketing of pharmaceutical products."[18] Harmonization of regulations can ensure favorable marketing conditions that can lead to early access to medicinal products and the promotion of competition and efficiency.[18] Both the FDA and MHRA are heavily involved in several international organizations including the International Council of Harmonization (ICH), the Pharmaceutical Inspection Co-operation Scheme (PIC/S), International Pharmaceutical Regulators Programme (IPRP), Asia-Pacific Economic Cooperation (APEC), and the International Coalition of Medicines Regulatory Authorities (ICMRA).[18]

PIC/S was established in 1995 as an extension of the Pharmaceutical Inspection Convention (PIC) of 1970.[11] The "scheme" was added to the name to emphasize that it is indeed an arrangement between Regulatory Authorities. PIC/S is a "non-binding co-operative arrangement between Regulatory Authorities in the field of GMP of medicinal products for human or veterinary use."[11] Any authority is allowed as long as it has a comparable GMP inspection system.[11] Currently, PIC/S has over "50 participating authorities throughout Europe, Africa, America, Asia, and Australia."[11]

PIC/S's current mission is "to lead the international inspection development, implementation, and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products."[11] They execute this mission by developing harmonized GMP standards, providing training opportunities to GMP inspectors, assessing GMP inspectorates, and enhancing networking between competent authorities thus increasing mutual confidence.[11] In addition to the above-mentioned opportunities, joining the scheme allows inspectorates to reap other benefits. This includes the sharing of information (i.e. GMP inspection reports), being a part of the PIC/S Rapid Alert and Recall System, and facilitating the conclusion of other agreements.[11] This leads to indirect benefits for the industry like the reduction of duplicate inspections, reduction of cost, facilitation of exportation, and enhanced market access.[12]

As noted earlier, the MHRA submits a capability assessment package to the FDA to be a recognized authority. Within that package is a reference to the PIC/S audit report. This is one of the many important PIC/S publications intended for inspectorates. The "PIC/S Audit Checklist – Interpretation Guide" details the scope of the Audit Checklist that includes MRA evaluations. The PIC/S Audit Checklist is also known as a GMP regulatory compliance program checklist. It is based on 11 components and 38 sub-components.[13] Each subcomponent is given a level of importance which is either Critical, Very Important, or Important. The subcomponents are then broken down into indicators. There is a total of 78 indicators.[13] Each of the indicators is given a method(s) of evaluation. The four methods of evaluation are "Documentation Review (DR), On-Site Evaluation at Inspectorate (OSEI), On-Site Evaluation at Laboratory (OSEL), and Observed Inspection (OI)."[12] The 11 components are the following: "(1) legislative and regulatory requirements and scope, (2) regulatory directives and policies, (3) GMP standards, (4) inspection

resources, (5) inspection procedures, (6) inspection performance standards, (7) enforcement powers and procedures, (8) alert and crisis system, (9) analytical capability, (10) surveillance program, and (11) quality management system."[12]

Although each component is relevant to the purposes of this paper, I will focus on the surveillance program inspection component due to the published FDA and MHRA inspection data. This component is divided into five subcomponents. They are "sampling and audit procedure, recall monitoring, consumer complaint system, adverse reaction reporting system/procedures, and medicinal product defect reporting system procedure."[12] There are two indicators within the first subcomponent of "sampling and audit procedure". The first indicator is as stated, "the market surveillance program for APIs and medicinal products is developed involving at least the inspection and laboratory departments using risk management principles and covers dosage forms of different medicinal product types."[13] PIC/S has three methods of evaluation for this indicator. The first is DR where there is verification of procedures on how the surveillance sampling plan takes place. The second method is OSEI and the third method is OSEL, providing verification of the surveillance program. The second indicator is concerned with the annual review of the surveillance program and that records of review are available.[13] This indicator is evaluated with the sample techniques as the previous indicator. The DR consists of a "comparison of the number of samples and analysis planned versus performed, a description of reasons for deviation, a review of results (in particular negative outcomes),"[13] and recommendations for next year's program.

The second subcomponent is for recall monitoring. There are five indicators that are referred back to the "enforcement powers and procedures" component. The first is a "provision for written notice of violations that are sent to the company."[13] The second is concerned with the

"recall procedures/mechanisms and records being made available."[13] The third is regarding the availability of GMP certificates and suspended/withdrawn GMP certificates, as well as the procedures of suspension/withdrawal. The fourth indicator is the way the inspectorate seizes products and that records are made available. The last indicator regarding recall monitoring is centered are prosecution procedures/mechanisms and those records availabilities. Each of the five indicators are evaluated in this same manner, with DR and OSEI.

The third subcomponent addresses the consumer complaint system, which PIC/S ranks critical in terms of importance. The first of four indicators in this subsection is the consumer complaint system procedures and records being made available. This indicator is evaluated with DR and OSEI. The second indicator is concerning issues of high risk being investigated immediately. This indicator is only evaluated by the OSEI method. This entails verifying a "formal documented system for the receipt, assessment and risk classification, and appropriate timelines for action."[13] The third indicator is concerned with the compliance staff and/or inspection staff being able to access complaint information. The fourth and final indicator is that "all product defects are reported, documented, and investigated."[13] The third and fourth indicators are evaluated via the OSEI method.

The fourth subcomponent "adverse reaction reporting system/procedures" is not evaluated because it is "not considered within the scope of a GMP regulatory compliance program."[13] The final subcomponent "drug product defect reporting system/procedures" has the same indicators as the "consumer complaint system" subcomponent. [13]

The "Standard Operating Procedure Team Inspection" is another important publication with regards to MRAs. There are numerous similarities between this SOP and the FDA and MHRA inspection process. This SOP applies to "GMP inspections of manufacturers located

inside and outside the PIC/S jurisdiction."[14] The SOP covers the preparation of inspections, the inspection itself, the inspection report, the GMP certificate, follow-ups, and documentation.[14] Similarly, with the FDA and MHRA, there is an opening meeting where the inspectors introduce themselves, "outline the purpose and scope of the inspection, and review the companies organizational structure, quality management system, and their activities."[14] The inspection protocols are also quite similar. For the FDA and MHRA, there is a plant tour, a focus on higher-risk activities, a review of the implantation of procedures, interviews of all personnel levels, and confirmation of the accuracy of the observed deficiencies[14]. Additionally, if there are critical deficiencies found, the inspectors will request immediate corrective and preventative measures. The closing meeting procedures, the report, and the timeline of follow-ups are also all very similar. One notable difference is the final inspection rating. PIC/S only has two possible ratings, conforming (C) or non-conforming (NC) with PIC/S GMP principles.[14]

The PIC/S "Guide to Good Manufacturing Practice for Medicinal Products" is an additional publication where many similarities can be seen compared to the FDA and MHRA inspection processes. There are a total of nine chapters in this document that exactly mirror the nine chapters of the Eudralex Volume 4 GMP Guidelines "Basic Requirements for Medicinal Products". The Eudralex Volume 4 GMP Guidelines contains the guidance for the interpretation of the principles and guidelines of GMPs for medicinal products for human and veterinary use.[15] These are the regulations that the European Medicines Agency (EMA) and MHRA follow and use to enforce inspections. Those nine chapters, in order, are "Pharmaceutical Quality System, Personnel, Premise and Equipment, Documentation, Production, Quality Control, Outsourced activities, Complaints and Product Recall, and Self Inspection."[14] The PIC/S Guide to GMPs and Eudralex Volume 4 both have substantial overlap to the FDA's GMP regulation, "Part 211

cGMPs for Finished Pharmaceuticals". For example, Part 211 directly addresses the personnel (including responsibilities of the quality control unit), facilities, equipment, production and process control, and documentation (including complaints).[16] These similarities illustrate the substantial efforts of harmonization of the FDA, MHRA, and PIC/S. These efforts can be noticed by the execution of such a complex MRA.

Lastly, the PIC/S publication and guidance titled "GMP Inspection Reliance" is the document that is most closely related to MRAs. It begins by explaining how important inspection reliance is because the "high demand for inspecting pharmaceutical manufacturing facilities far exceeds what any one National Competent Authority (NCA) can accomplish."[19] The purpose of the document is to outline a "process for remote assessment of GMP compliance of overseas facilities to confirm where an acceptable level of GMP compliance can be identified from activities of another regulatory authority, thus avoiding the need for an onsite inspection."[19] This document only outlines high-level guidance to allow for details of the process to vary between regulatory authorities. The guidance also attempted to aid inspectorates in making optimal use of inspection resources.

With regards to the scope of the guidance, the procedures are "limited to manufacturing facilities in territories where assurance has been gained of the capability of the hosting NCA."[19] This can be determined in three different ways. The first being the territory where the facility is located is within a PIC/S Participating Authority. The second way is "the hosting NCA has been assessed in the last five years utilizing a robust assessment tool"[19] and resulted in a positive outcome. The third is the presence of an "MRA in place between the two countries that covers GMP."[19]

The process is broken into four different sections, the introduction, establishing country reliance, assessment of site compliance, and monitoring/reviewing. Within the introduction, it states that the framework in this document is used to establish regulatory authorities' own procedures. It then states how within the procedure there needs to be information about "triggers and risk factors that would result in an inspection being required, and how the assessment and outcome should be recorded."[19] Both of these are clearly emphasized in the FDA's and MHRA's risk-based approach and reporting styles.

According to PIC/S, establishing country reliance can be done in two ways. The first simply is that "the hosting NCA is a PIC/S Participating Authority."[19] The latter is "the requesting NCA undertakes an assessment of the hosting NCA using the JAP (Joint Audit Program)/JRP (Joint Reassessment Program) or a similarly robust assessment tool."[19] The "assessment of site compliance" section within the process is organized into four subsections. The first is "gathering information". The first step is to obtain the GMP certificate issued by the hosting authority or at a minimum the "most recent inspection of the manufacturing site by the hosting authority."[19] There may be additional information that will be requested. This includes specific information on the latest inspection "(dates on-site, inspection scope and outcome, company response/CAPA plan, and planned re-inspection date if known)."[19] There should be post-inspection information provided along with "information relating to inspections by other regulatory authorities in a defined time (e.g. previous two years or since the previous inspection by the regulatory authority performing the assessment)."[19] Lastly, a site master file and information aiding in the risk assessment should be requested. There is an emphasis on a risk-based approach. Addition information can always be requested, as appropriate.

The second subsection within the assessment of site compliance section is "assessment and outcome". The purpose of this is "to gain assurance that GMP compliance has been established by the hosting NCA and that there is no new evidence gathered that would warrant an onsite inspection."[19] This assessment should be documented and includes the following minimum information: "what documentation was reviewed and by whom, the outcome of the assessment, and the rationale for the decision."[19] The outcome of the assessment "should also be communicated to the manufacturing site and if possible to the hosting NCA."[19] If the decision has been made that an onsite inspection is not required, inspectorates may choose to issue a GMP certificate referencing the process of remote review.[19]

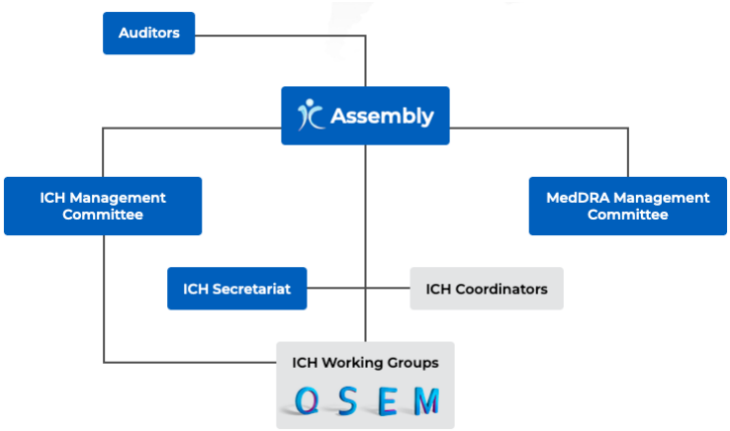
The third subsection within the assessment of site compliance section is "triggers and risk factors for an onsite inspection".[19] This section provides examples (not limited to) of possible triggers or risk factors.[19] This includes "failure of the site to supply the requested information, no previous inspection history of the site, the site is not licensed by the hosting NCA, and there is evidence that another NCA has not approved the facility (or even aspects of it)."[19] The final subsection within the assessment of site compliance section is concerned with additional considerations. The final section within the process portion of this guidance is "monitoring and reviewing". It simply states that after undertaking the remote inspection, the site should be maintained within the inspection program to ensure periodic review.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is another organization that has a different purpose and scope of regulatory harmonization compared to PIC/S. Since 2015, it has been reformed as an international non-profit association. Its focus is "bringing together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and

develop ICH guidelines."[20] The organization was originally founded in 1990, since then it has evolved to work with the increasing globalization of drug development. The mission of ICH is "to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner."[20] ICH executes this mission through the "development of ICH guidelines via a process of scientific consensus with regulatory and industry experts."[20]

There are two types of ICH association participants, members or observers. As of December 2021, ICH has a total of 19 members. There are three founding regulatory members which are the EC (Europe), the MHLW/PMDA (Japan), and the FDA (United States). Now, there are several other regulatory members. There are three founding industry members. They are "EFPIA (European Federation of Pharmaceutical Industries and Associations), JPMA (Japan Pharmaceutical Manufacturers Association), and PhRMA (Pharmaceutical Research and Manufacturers of America)."[21] The WHO (World Health Organization) and IFPMA (International Federation of Pharmaceutical Manufacturers and Association) are standing ICH observers, along with 33 other observers.[21] The composition of ICH's 34 working groups is diverse with a total of 762 experts. The structure of ICH is illustrated below.

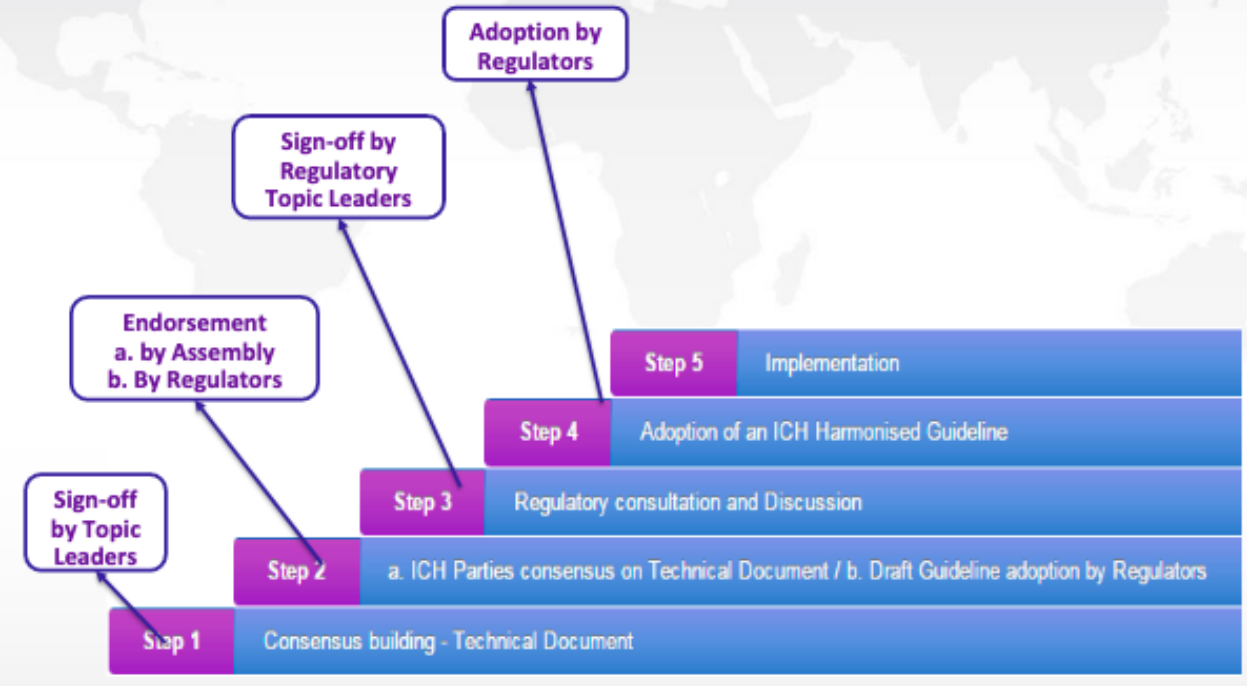
Figure 4: Structure of ICH[22]



The “Assembly” is the overarching body of the Association.[21] It is composed of “all members that make decisions on articles of Association, rules of procedures, admission of new members, and adoption of ICH guidelines.”[21] Decisions are made by consensus and if there is no consensus, only regulatory members have the right to vote.[21] There are certain criteria for both regulators and industry to be a part of the Assembly. The "Management Committee" is the “body that oversees operational aspects of the Association on behalf of all members, including administrative matters, financial matters, and the oversight of the working groups.”[21] The Management Committee “provides recommendations on the selection of new topics for harmonization as well as the adoption, withdrawal, or amendments of ICH guidelines.”[21]

ICH follows a five-step process for the development of its guidelines.[21] The first step is for the working group “to prepare a consensus draft of the technical document.”[21] Next, “the members of the Assembly are invited to endorse the technical document.”[21] This is then followed by “regulatory members of the Assembly being invited to endorse the draft guideline.”[21] The third step in the process is the “public consultation by regulatory members and secretariat where all comments are then considered by the working group.”[21] This step in the process is completed once consensus is reached by the regulatory experts of the working group.[21] The fourth step is the adoption of the final ICH harmonized guideline by regulatory members of the Assembly.[21] The fifth and final step is the implementation of the technical document by ICH regulatory members. The following figure illustrates this process.[21]

Figure 5: ICH Process for Development of Guidelines[21]



Currently, ICH has produced nearly 70 guidelines on technical requirements on safety (15), quality (24), efficacy (21), and multidisciplinary (8).[21] Additionally, they have produced the following standards: the Electronic Standards for the Transfer of Regulatory Information (ESTRI), the CTD/eCTD (electronic Common Technical Document), and MedDRA (standardized medical terminology).[21] For this thesis, the focus will reside on the quality guidelines as they are closely related to the FDA-MHRA MRA. These include guidelines on "stability studies, defining relevant thresholds for impurity testing, and a more flexible approach to pharmaceutical quality based on GMP risk management."[23] The most relevant guidelines with regards to the MRA, thus the most important to discuss are ICH Q7 "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" and ICH Q10 "Pharmaceutical Quality System". It is worth noting both are fully implemented by the FDA and MHRA.

The first eight chapters of ICH Q7 are nearly identical to the previously discussed Eudralex Vol. 4 regulations and the PIC/S "Guide to Good Manufacturing Practice for Medicinal Products" and very similar to the FDA's Part 211 regulations. Interestingly, in the ICH Q7 later chapters, you can see more organizational similarities with FDA regulations compared to PIC/S and Eudralex. For example, ICH Q7 and Part 211have specific chapters for "laboratory controls", "holding/storage and distribution", and "rejection and re-use of materials/returned and salvaged drug products". Based on these similarities and differences, you can see the participation of all ICH participants and a clear attempt to harmonize with different regulatory agencies.

The guidance is clear in the "Chapter 1 Introduction" regarding the objective, regulatory applicability, and scope. The objective of ICH Q7 is intended to “provide guidance regarding GMP for the manufacturing of APIs (active pharmaceutical ingredients) under an appropriate system for managing quality while ensuring the APIs meet the requirements for quality and purity.”[24] A topic of debate throughout the pharmaceutical industry has been when in the process of API manufacturing is a material considered an API. This guidance states that this guidance is only applied when the “material is classified as an API in the region or country in which it is manufactured or used in a drug product.”[24] The guidance applies to the “manufacturers of APIs for use in human drug/medicinal products.”[24] It does exclude “vaccines, whole cells, whole blood and plasma, blood and plasma derivatives, and gene therapy APIs.”[24] This is also seen within the scope of the FDA/MHRA MRA, proving the need for improvement of regulatory harmonization in these areas.

The only other chapter in Q7 that will be described is "Chapter 2 Quality Management". The five subsections are “principles, responsibilities of the quality unit(s), responsibility for production activities, internal audits (self-inspection), and product quality review.”[24] The

principle subsection lays the foundation for the chapter stating that quality is the "responsibility of all persons involved in manufacturing."[24] It stresses the importance of establishing, documenting, and implementing an effective system for managing quality involving management and the entire organizational structure.[24] Furthermore, it states that "all quality activities should be documented at the time they are performed"[24], and any deviations should be documented, explained, and investigated if needed.[24] The second subsection "responsibilities of the quality unit(s)" has similarities compared to the first subsection. The quality unit(s) "should be involved in all quality-related matters and should review/approve all appropriate quality-related documents."[24] It then goes into the 15 main responsibilities that a quality unit should have at a minimum.

The responsibility for production activities subsection is similar in terms of format to the quality unit subsection. It lists 10 minimum responsibilities. The internal audits subsection is brief but emphasizes that these self-inspections should be regular and performed per an approved schedule.[24] The findings and corrective actions should be documented and brought to management where "agreed corrective actions will then be completed in a timely and effective manner."[24] The final subsection "product quality review" first states that "regular quality reviews of APIs should be done to verify the consistency of the process."[24] The subsection list 7 areas that reviews should cover. Another common theme in terms of quality and regulatory harmonization is a review of all critical deviations/non-conformances, related investigations, and the adequacy of corrective actions.

The ICH Q10 "Pharmaceutical Quality System" is described as "a model for an effective quality management system (or pharmaceutical quality system) for the entire pharmaceutical industry."[25] The guidance has four main chapters which are: "pharmaceutical quality system

(PQS), management responsibility, continual improvement of process performance and product quality, and continual improvement of the PQS."[25] The first chapter PQS has an introduction section describing the background of the guidance. The comprehensive model is based on International Standards Organization (ISO) quality concepts and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management".[25] It is not intended to "create any new expectations beyond current regulatory requirements."[25] A unique aspect of ICH Q10 is that the model "can be implemented throughout the different stages of a product lifecycle."[25] The guideline has a very transparent scope with an explanation of the product lifecycle. It states that "the product lifecycle includes the following technical activities for new and existing products: pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation."[25] Each activity has specific examples within it.

In the first chapter is a subsection titled "relationship of ICH Q10 to regional GMP requirements, ISO standards and ICH Q7". It describes ICH Q7 (as well as ISO quality management system guidelines) being the foundation for ICH Q10.[25] As ICH Q10 is a harmonized model for PQS, it is "intended to be used with regional GMP requirements."[25] ICH encourages "the use of science and risk-based approaches at each lifecycle."[25] This is similar to the FDA and MHRA approach, however, ICH promotes "continual improvement across the entire product lifecycle."[25] ICH identifies room for growth with regards to harmonizing the risk-based approach many regulators are implementing.

Another relevant section to the FDA-MHRA MRA is the subsection titled "relationship of ICH Q10 to regulatory approaches". It states that the regulatory approach "should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the PQS."[25] Additionally, it points out that "the

effectiveness of the PQS normally can be evaluated during regulatory inspections at the manufacturing site."[25] In the table below, ICH also identifies opportunities that can further enhance science and risk-based approaches.

Table 3: Potential Opportunities to Enhance Science and Risk-Based Regulatory Approaches[25]

Scenario	**Potential Opportunity**
Comply with GMPs	Compliance- status quo
• Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g. Q9 and ICH Q10).	• Increase use of risk-based approaches for regulatory inspections.
• Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	• Facilitate science-based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms
• Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9 and ICH Q10).	• Increase use of risk-based approaches for regulatory inspections; • Facilitate science-based pharmaceutical quality assessment; • Optimize science and risk-based post-approval change processes to maximize benefits from innovation and continual improvement; • Enable innovative approaches to process validation; • Establish real-time release mechanisms.

Within Chapter 1 PQS, ICH explains the three main objectives of ICH Q10. They are to achieve product realization, establish and maintain a state of control, and facilitate continual improvement. ICH Q10 also has a section within the PQS chapter dedicated to quality risk management. It states that quality risk mangement is integral to an effective PQS and can provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. For further information on quality risk management, ICH Q9 provides principles and examples of tools for quality risk management.

The second chapter, management responsibility, is comprised of the following eight subsections: "management commitment, quality policy, quality planning, resource management, internal communication, management review, management of outsourced activities and purchased materials, and management of change in product ownership."[25] ICH recognizes "leadership is essential to establishing and maintaining a company-wide commitment to quality and the performance of the PQS."[25] The third chapter, continual improvement of process performance and product quality, is comprised of two major sections with several subsections within them. The two sections are lifecycle stage goals and PQS elements. According to ICH Q10, the four elements to the PQS are: "process performance and product quality monitoring systems, corrective action and preventative action (CAPA) system, change management system, and lastly management review of process performance and product quality."[25] The following table summarizes the application of the PQS elements throughout the product lifecycle.

Table 4: Application of the PQS Elements Throughout the Product Lifecycle[25]

	Pharmaceutical Development	**Technology Transfer**	**Commercial Manufacturing**	**Product Discontinuation**
Process performance and product quality monitoring systems	Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

CAPA system	Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.
Change management system	Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.
Management review of process performance and product quality	Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

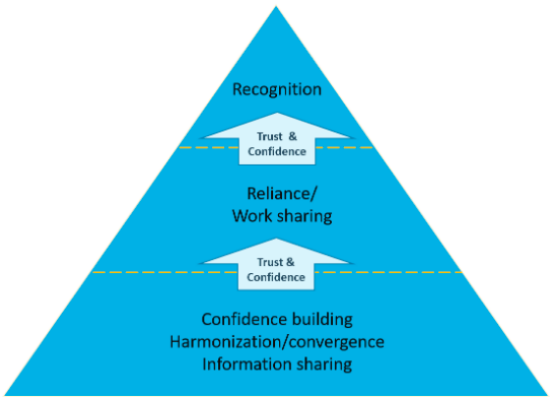
The final chapter of ICH Q10, continual improvement of the PQS, focuses on "the management review of the PQS, monitoring of internal and external factors impacting the PQS, and the outcomes of management review and monitoring."[25]

It would be misleading to discuss ICH Q7 and ICH Q10 without discussing the key integration of both Q8 and Q9. ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management" both leave a mark in ICH Q10. ICH Q8 describes processes for

pharmaceutical development and provides for robust development and understanding that creates a foundation for continual improvement.[26] It contains key linkages to product realization within the PQS. ICH Q9 facilitates the use of quality risk management approaches throughout the PQS by aiding in appropriate risk management principles and methods.[26]

In conclusion, there cannot be MRAs without a strong foundation of harmonization. Harmonization could not be achieved without the important effort and work of both PIC/S and ICH. The following figure demonstrates how trust and confidence are necessary for any form of cooperation between regulatory authorities, all the way from reliance to recognition.[27] The dotted lines illustrate the fluidity for regulatory authorities in activities such as information sharing in order to build the crucial trust needed for demonstrating equivalence.[27]

FIGURE 6: Building Confidence and Trust from and for Greater Reliance[27]



CHAPTER 4

GMP ENFORCEMENT ACTION DATA

The best approach for analyzing the potential effects of an MRA is to analyze and trend GMP enforcement action data. I analyzed the data using two different scopes. It can be a very narrow scope of analyzing and trending individual observations and deficiencies from each agency to identify similarities and differences in the inspection process. The goal of this approach would be to identify the potential priorities of both agencies and to analyze how equivalent each agency truly is concerning the inspection process. Alternatively, there can be a wider scope of analyzing and trending the number of inspections each agency has performed and where those inspections were located. As previously discussed, the goal of an MRA agreement is to yield greater efficiencies for the regulatory agencies to reallocate potential resources. This wider scoped approach would help identify whether the two agencies are truly reaching the goal of yielding greater efficiencies and the reallocation of agency resources.

The FDA-MHRA MRA was only fully implemented in 2019. Statistically, three years of data is required to trend. Thus, using either approach to identify effects of the FDA-MHRA MRA is not currently possible. The MHRA has only published their 2018 and 2019 GMP deficiency data. They do have published summaries (in PowerPoint format) of 2010, 2012, 2013, and 2015 data. The 2020 data has been delayed due to the COVID-19 Pandemic. The FDA is much more transparent. They have detailed inspectional observation data sets (in spreadsheet format) published every year from 2006 to 2021. The FDA describes it as “not a comprehensive list of all inspectional observations but rather representative of the area of regulation and the

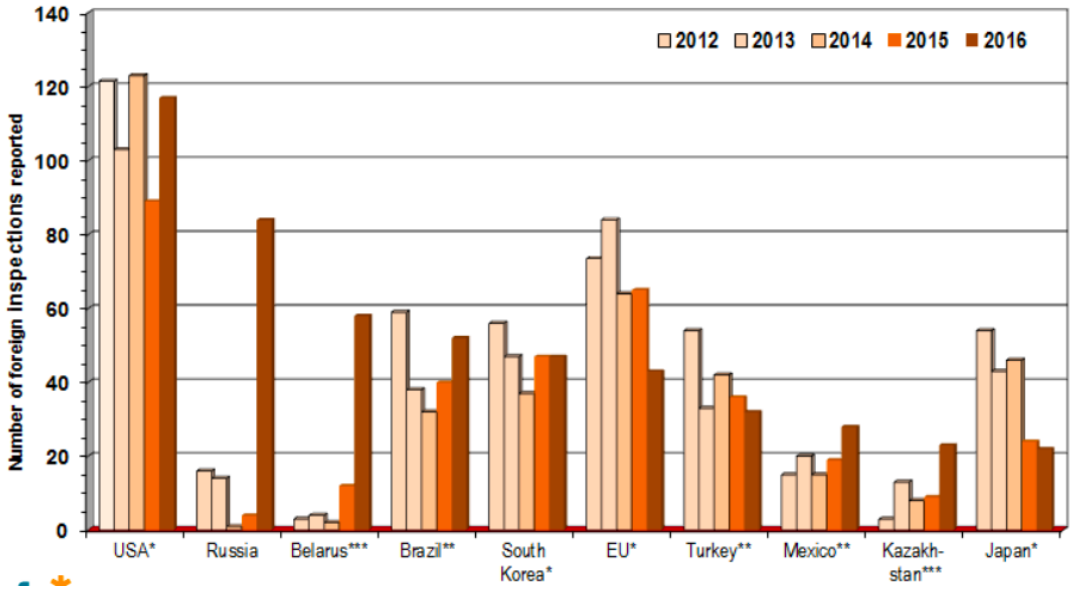
number of times it was cited as an observation on an FDA Form 483 during an inspection conducted by the FDA."[31]

In the wider scope, the consensus effect of a well-functioning MRA would be to see an increase in domestic inspections while seeing a decrease in foreign inspections. An excellent resource for this focus is the EFPIA (European Federation of Pharmaceutical Industries and Associations) Annual Regulatory GMP/GDP Inspection Survey. Starting in 2003, EFPIA surveyed member companies to map the level of GMP inspections performed at each of their manufacturing sites.[28] One disadvantage of the EFPIA Inspection survey, for this report, is that the UK/MHRA is grouped into the EU category and typically is not analyzed separately. Additionally, the only data included comes from industry members who participate in the survey.

Interestingly, the intention of the EFPIA Inspection Survey has evolved in recent years. In 2016, it was the intent to "demonstrate opportunities for mutual reliance, collaboration, and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections."[29] EFPIA wanted to demonstrate the "benefits of PIC/S membership in optimizing the use of inspection resources while maintaining patient safety."[29] Since then the intentions have evolved to the following: "(1) monitor trends and new focus areas of GMP/GDP inspections and ISO-certifications, (2) continue to promote reliance, collaboration, and consistency in inspections by highlighting duplicate regulatory GMP/GDP inspections and ISO-certifications, and (3) materialize the benefits of PIC/S membership in optimizing the use of inspection resources with a harmonized risk-based approach for inspections while maintaining patient safety."[30] This shift in priorities may be due to the implementation of MRAs and the substantial efforts that have already been made in regulatory harmonization.

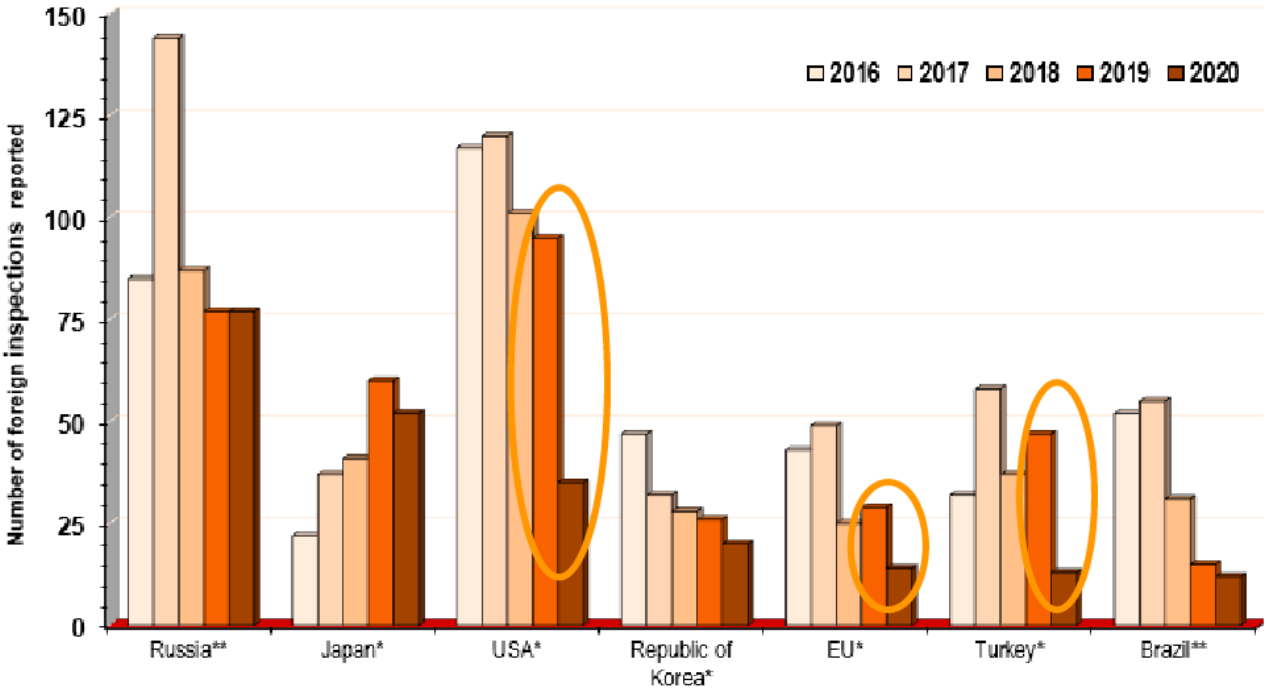
One way to analyze the two agencies' attempt for greater efficiency is to analyze the number of foreign inspections performed. Figure 7 and Figure 8 illustrate the number of foreign inspections performed by each country surveyed. Notice the MHRA is grouped into the EU category. Figure 7 shows the number of inspections from 2012-2016, all years before the signing of the FDA-MHRA MRA. Notice the FDA has by far the most foreign inspections throughout all five years, with over 120 inspections performed in 2012 and 2014. There are only two other instances of any other country reaching over 80 inspections performed in a single year. Additionally, there is no clear sign of a significant reduction of foreign inspections by the FDA. There was a significant decrease in 2015 however, that can be attributed to the US government shutdown. Alternatively, the EU generally has performed the second most foreign inspections but there is a decrease by 2016. This drop can potentially be attributed to the efforts of PIC/S and the strong partnerships throughout the EU.

Figure 7: Number of Foreign Inspections Performed by Country 2012-2016[29]



Looking at figure 8 and into 2020, you can notice several changes. After a slight increase in 2017, the FDA has shown a reduction in foreign inspections in 2018, a year after signing the MRA with the EU. There is then a massive reduction in FDA foreign inspections in 2020 with roughly 30 foreign inspections performed. This is attributed to the COVID-19 pandemic and the inability to travel overseas. However, it can also speak to the increase in trust between the FDA and other agencies, including the MHRA. The EU has shown a massive reduction in foreign inspections with roughly 65 foreign inspections performed in 2015 to approximately 25 foreign inspections in 2019 (before the COIVD-19 pandemic). It seems that MRAs and the work of PIC/S have greatly increased the efficiency of the European Medicines Agency (EMA), including the MHRA.

Figure 8: Number of Foreign Inspections Performed by Country 2016-2020[30]



Another aspect of analyzing the potential effects of the MRA is looking at "the evolution of the number of foreign inspections versus the number of manufacturing sites."[32] EFPIA has

found (from 2006-2017) that the "number of foreign inspections doubled while the number of manufacturing sites remained relatively constant."[32] As seen in Figure 9, there were roughly 600-850 manufacturing sites throughout those years. There were roughly 350 foreign inspections in 2006 compared to roughly 750 in 2017. This data demonstrates the vastly inefficient inspection process of all regulatory agencies and the need for MRAs and regulatory harmonization. As seen in Figure 10, in 2018 (a year after the FDA-EU MRA was signed) there was a sharp decrease in the number of foreign inspections. Although the MRA was not fully implemented and was still in the transition phase, it appears it had a quick effect on the number of foreign inspections performed.

Figure 9: Number of Foreign Inspections versus Manufacturing Sites (2006-2017)[32]

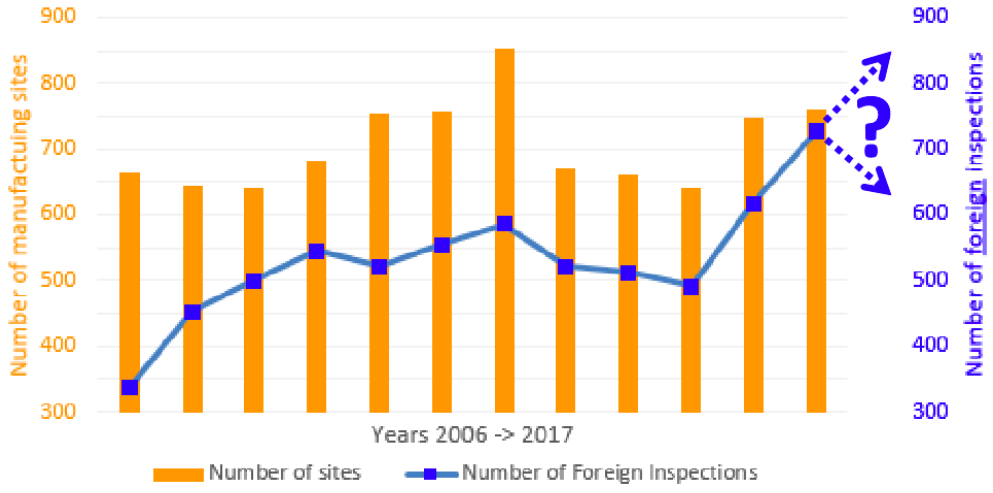
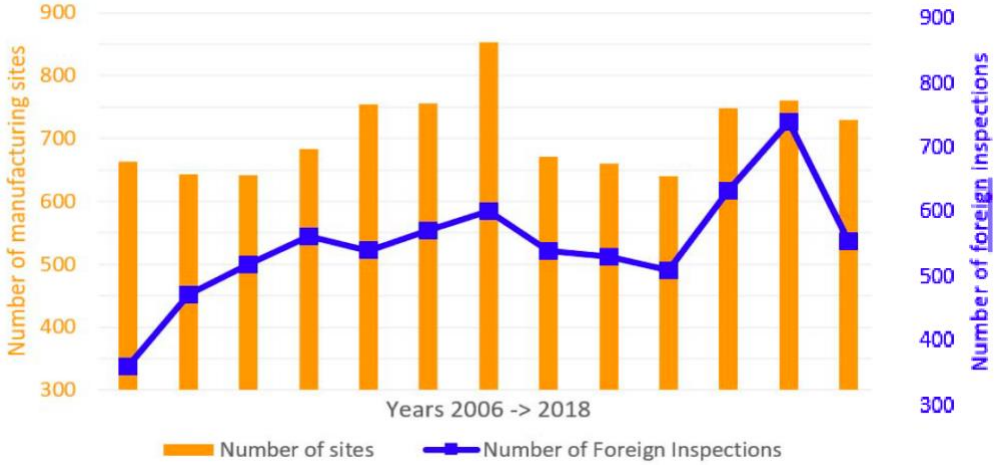


Figure 10: Number of Foreign Inspections versus Manufacturing Sites (2006-2018)[33]

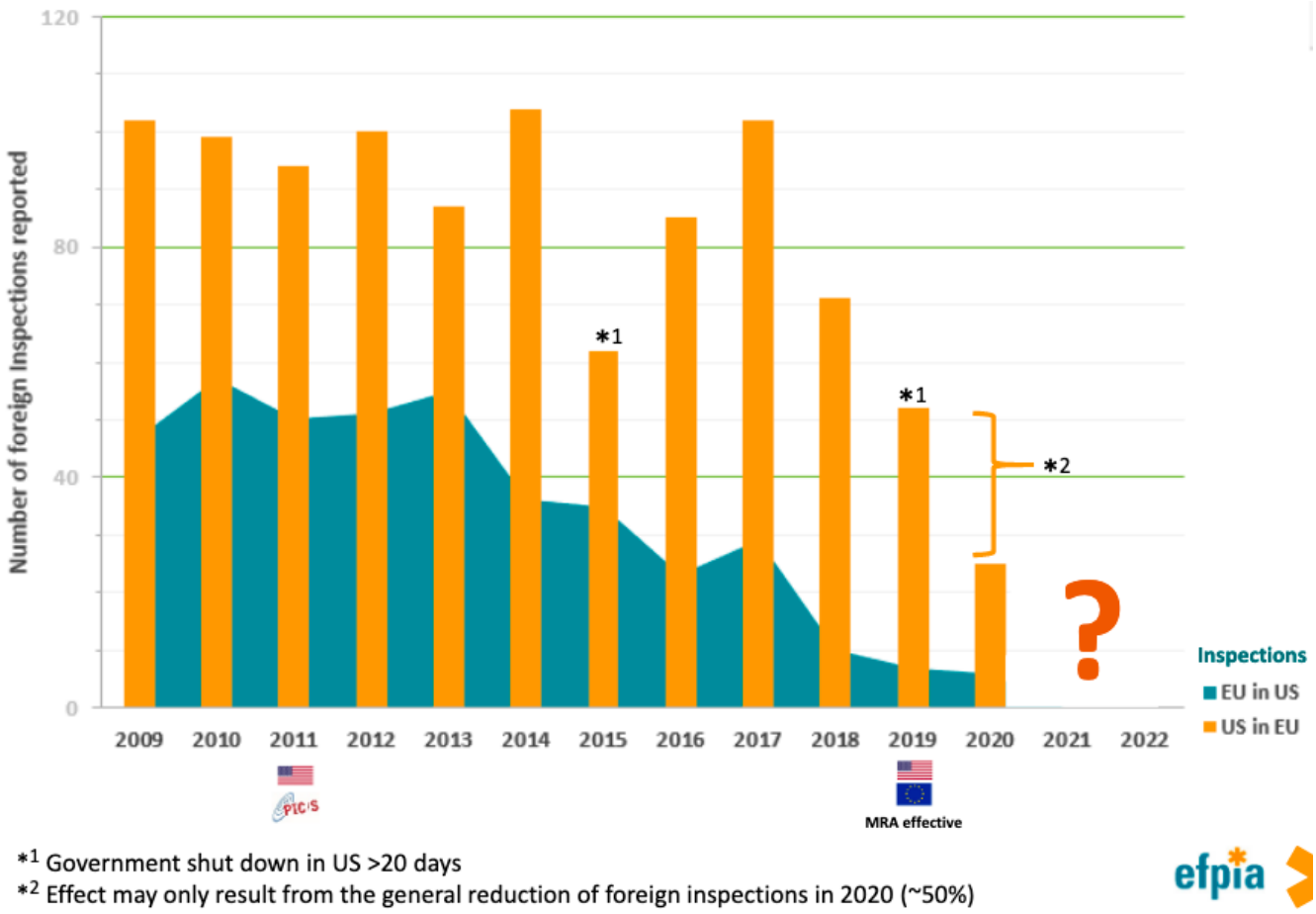


The 2020 EFPIA Inspection Survey directly compares the number of US foreign inspections performed by the EU versus the number of EU foreign inspections performed by the US, as seen in Figure 11. The trending of this data aims to demonstrate the effectiveness of both PIC/S and the MRA by proving an increase in efficiency and a reduction in agency resources. Similar to the trend in Figure 7 and Figure 8, there is a sharp decrease in US inspections in the EU after 2017 (signing of MRA) and 2019 (full MRA implementation). It must be noted that this effect in the data in 2020 may only be the result of the general reduction of foreign inspections due to the COVID-19 pandemic. Similarly, in 2015 and 2019 the US had a government shutdown that potentially affected the data. For these reasons, more years of data are still needed to draw accurate conclusions of the effects of the FDA-MHRA MRA.

Intriguingly, the EU inspections in the US dropped sharply in 2013 after the FDA joined PIC/S in 2011 and there is no significant decrease in EU inspections in the US after the MRA was fully implemented. It seems that the US joining PIC/S had a much larger impact on the number of EU (and thus MHRA) inspections in the US than the implementation of the MRA. However, the US

inspections in the EU seem to be affected oppositely based on the trend seen in the previous paragraph. It appears that the MRA implementation had a larger impact than the joining of PIC/s on US inspection in the EU based on the 2019 data.

Figure 11: Number of US Inspections Performed by EU versus Number of EU Inspections Performed by US[30]



In addition to trending foreign inspections, the 2017 and 2019 EFPIA Inspection Surveys trend the number of domestic inspections reported in the survey as seen in Figures 12 and 13, respectively. In both years, the EU doubled the number of domestic inspections compared to the US. This large number of EU inspections may signify a greater priority on domestic inspections speaking to the trust within MRAs and PIC/S. Since this is only the EFPIA survey results as

opposed to the total data from the agencies, it is difficult to draw any definite conclusions. Both the EU and US have a slight decrease in the number of domestic inspections, with the US having a larger decrease between the two.

Figure 12: Number of Domestic Inspections Reported in 2017[32]

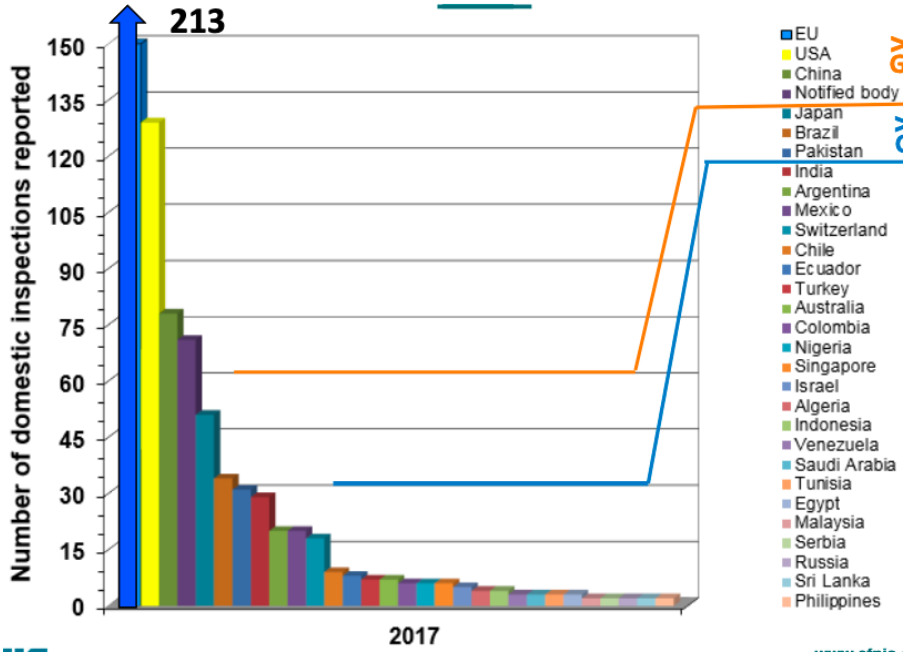
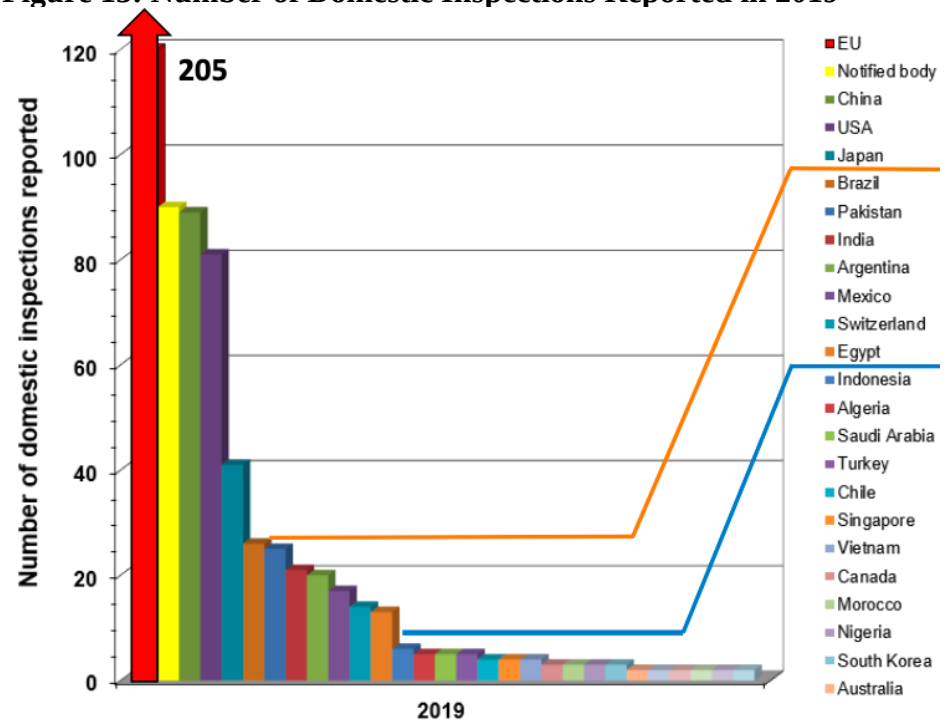
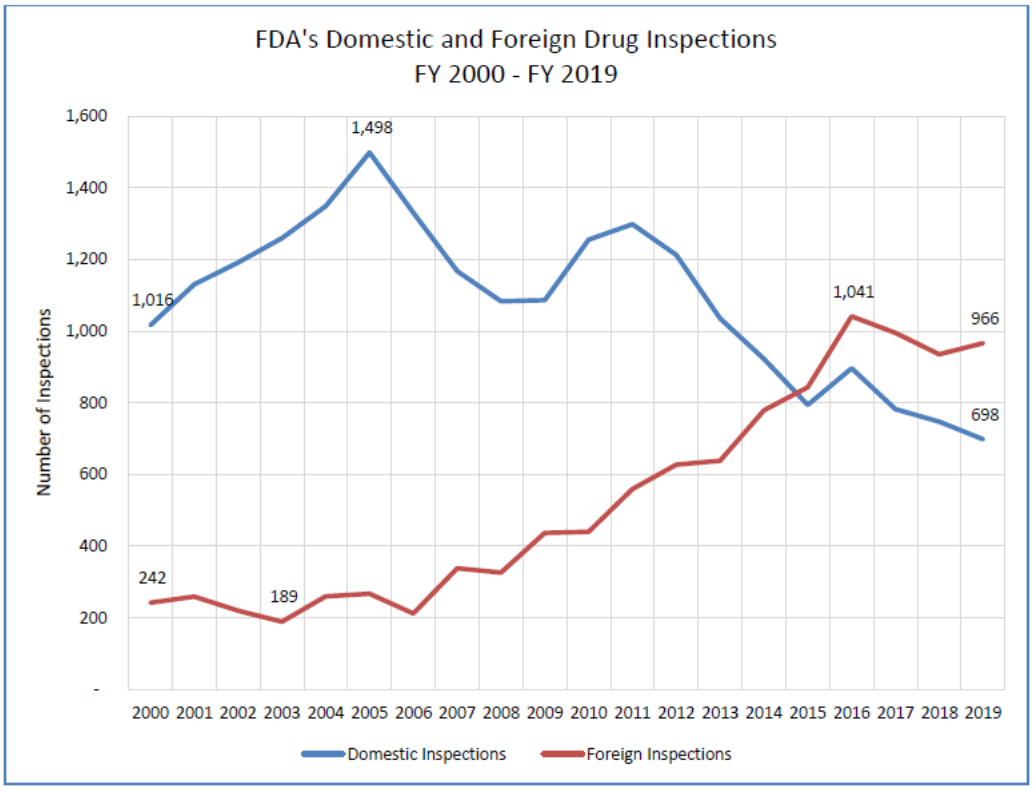


Figure 13: Number of Domestic Inspections Reported in 2019[34]



As previously mentioned, the FDA provides great transparency with their inspection data. Figure 14 shows the total number of domestic and foreign inspections from 2000-2019, providing a large timeline to trend. Starting in 2006, the FDA had a sharp increase in foreign inspections most likely due to mounting pressure outside the FDA to be more thorough on overseas facilities. In 2015, the number of foreign inspections finally exceeded the number of domestic inspections.[35] Notice in 2015 there is a slight decline in both domestic and foreign inspections which might be attributed to the new risk-based approach. The downward trend in domestic inspections was also seen in the EFPIA survey, however, less so in the foreign inspections. This is most likely due to the small sample size in the EFPIA survey.

Figure 14: FDA Domestic and Foreign Drug Inspection Trending (2000-2019)[35]



The MHRA had much less data available as seen in Table 5. Starting in 2015, the MHRA began releasing the number of domestic and foreign inspections, with the exception of 2017. In previous years, they released the number of total inspections, but only elaborated on the location of Major/Critical deficiencies. Interestingly in 2018, they provided specific overseas locations that were inspected, however, did not do so in 2019. The total number of inspections peaked in 2016 with a substantial decrease by 2019. The percent of domestic inspections had risen from 74% in 2015 to 88% in 2019 and the number of foreign inspections has decreased from 26% to 12%. This effect seems to coincide with the goals of the MRA suggests it was having a positive effect already. Since the MHRA only inspected five sites in the US, it is difficult to determine if the MRA resulted in a decrease in MHRA inspections in the US. Lastly, it is worth noting the MHRA has put a huge priority on inspecting sites in India with "approximately 75% of inspections conducted outside the U.K. being in India."[36]

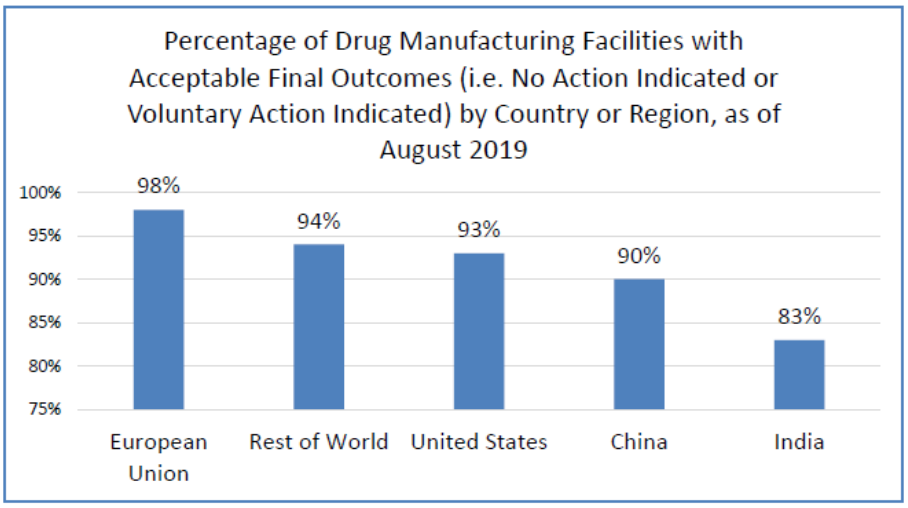
Table 5: MHRA Domestic and Foreign Drug Inspection Trending (2015, 2016, 2018, 2019)[36]

Country	Number of Inspections 2015 / % total	Number of Inspections 2016 / % total	Number of Inspections 2018 / % total	Number of Inspections 2019 / % total
Total	303	324	285	258
U.K.	224 / 74%	242 / 75%	228 / 80%	228 / 88%
Overseas Inspections	79 / 26%	82 / 25%	57 / 20%	30 / 12%
India			43 / 15%	
China			5 / 2%	
United States			5 / 2%	
Bangladesh			1 / 0.3%	
South Korea			1 / 0.3%	
Singapore			1 / 0.3%	
Japan			1 / 0.3%	

Figure 15 illustrates the percentage of drug manufacturing facilities with acceptable final outcomes by country/region in 2019 demonstrating that most manufacturing sites were considered acceptable (No Action Indicated or Voluntary Action Indicated).[35] Notice India had a

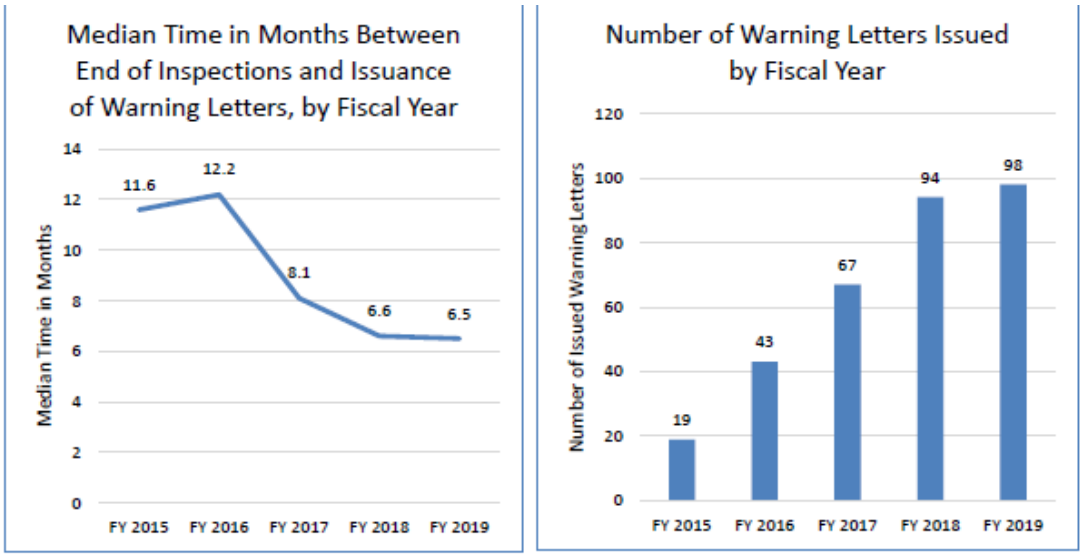
lower approval rate compared to every other location. This demonstrates that the FDA and MHRA had similar concerns with sites located in India. An important aspect of the MRA was to reallocate resources to areas of greater concern. The data shows that both agencies began to do so perhaps because of the effectiveness of the MRA, however, it is still too early to tell.

Figure 15: FDA Percentage of Acceptable Final Outcomes by Country or Region[35]



The FDA has published a unique aspect of their GMP inspection that is directly related to its inspection efficiency. It is hard to decipher if this increased efficiency had much to do with the MRA or harmonization in general but does show that the FDA is working towards the goal of increasing inspection efficiency. "From FY 2015 to FY 2019, the FDA had an overall 44% improvement in median time between the end of an inspection and the issuance of warning letters."[35] There was also a huge increase in the number of warning letters in this same period, with only 19 issued in FY 2015 to 98 issued in FY 2019 (shown in Figure 16).

Figure 16: FDA's Increasingly Efficient Inspection Process[35]



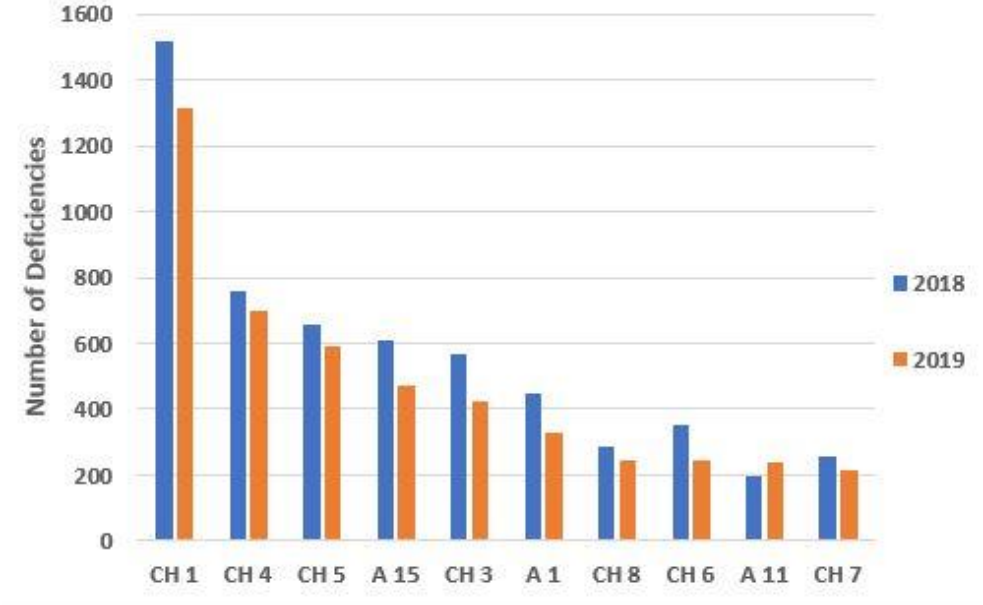
Although there is not enough data to trend potential effects of the MRA in the previously described narrow scope, it is still worth analyzing individual observations and deficiencies from each agency to potentially identify similarities and differences in priorities during inspections of both agencies. If the two agencies are willing to accept each other's inspection results, they should have somewhat similar priorities when adhering to cGMP regulations. Similar to the EFPIA survey, a great resource for this narrow scope comes from the website pharmaceuticalonline.com which posts articles related to the pharmaceutical industry. Barbara Unger has posted several articles related to both MHRA and FDA inspection trends. Ms. Unger has extensive expertise within GMP auditing and regulatory intelligence services.[36] Table 6 which is taken from one of Ms. Unger's articles illustrates the MHRA trend of the top ten areas of all deficiencies from 2015-2019, excluding 2017. The first thing to notice is that quality systems top the list all four years. Additionally, there was no change in the top six categories from 2018 to 2019 and all of the chapters/annexes in the top 10 for 2018 were among that same group in 2019.[36]

Table 6: MHRA List of Top 10 Areas of all Deficiencies (2015, 2016, 2018, 2019)[36]

Rank	2015	2016	2018	2019
1	Quality Systems	Quality System	Quality System	Quality Systems
2	Complaints and Recalls	Sterility Assurance	Documentation	Documentation
3	Documentation	Production	Production	Production
4	Quality Control	Complaints and Recall	Validation / Qualification	Validation / Qualification
5	Computerized Systems	Qualification / Validation	Premises and Equipment	Premises and Equipment
6	Production	Premises and Equipment	Sterility Assurance	Sterility Assurance
7	Premises and Equipment	Computerized Systems	Quality Control	Complaints and Product Recall
8	Validation	Personnel	Complaints and Recall	Quality Control
9	Personnel	Documentation	Outsourced Activities	Computerized Systems
10	Materials Management	Quality Control	Computerized Systems	Outsourced Activities

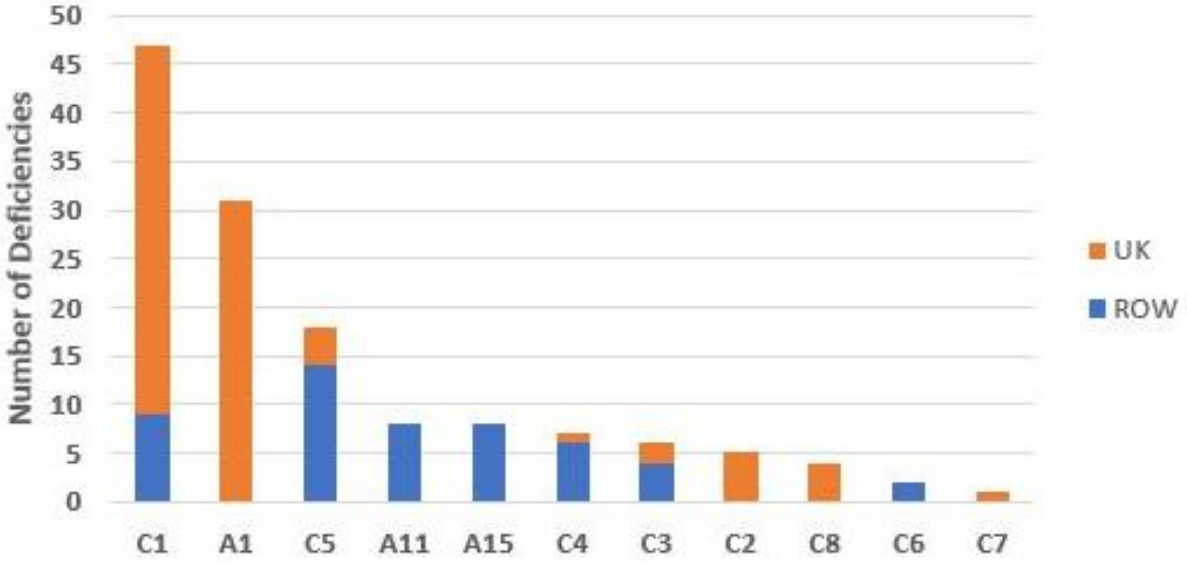
Figure 17 contains the same list from above, except it depicts only 2018 and 2019 and includes the numerical values. It is worth noting that all deficiency classifications (critical, major, and other) were included in this figure. Figure 17 demonstrates the great priority the MHRA has on the quality system as it has more than twice the number of deficiency citations as the next nearest chapter.[36] Furthermore, there is a general pattern of decreasing number of deficiencies in each area in 2019 compared to 2018.

Figure 17: MHRA Data of Top 10 Areas of All Deficiencies (2018, 2019)[36]



Ms. Unger also compares 2019 critical deficiencies by domestic or foreign location. These numbers compare the MHRA priorities of domestic inspections versus foreign inspections. Figure 18 illustrates this comparison. An area to notice from this comparison is Chapter 5 "Production". Not seen in Figure 218is the fact that the number of critical deficiencies in Chapter 5 doubled compared to 2018. In 2019 the vast majority of these deficiencies were in sites overseas. This is particularly intriguing because only 12% of inspections were conducted outside of the U.K., suggesting there is a big emphasis on production in overseas sites. Only Annex 11 (Computerized Systems) and Annex 15 (Qualification and Validation) had critical deficiencies overseas and none within the U.K.

Figure 18: MHRA 2019 Critical Deficiencies by Country[36]



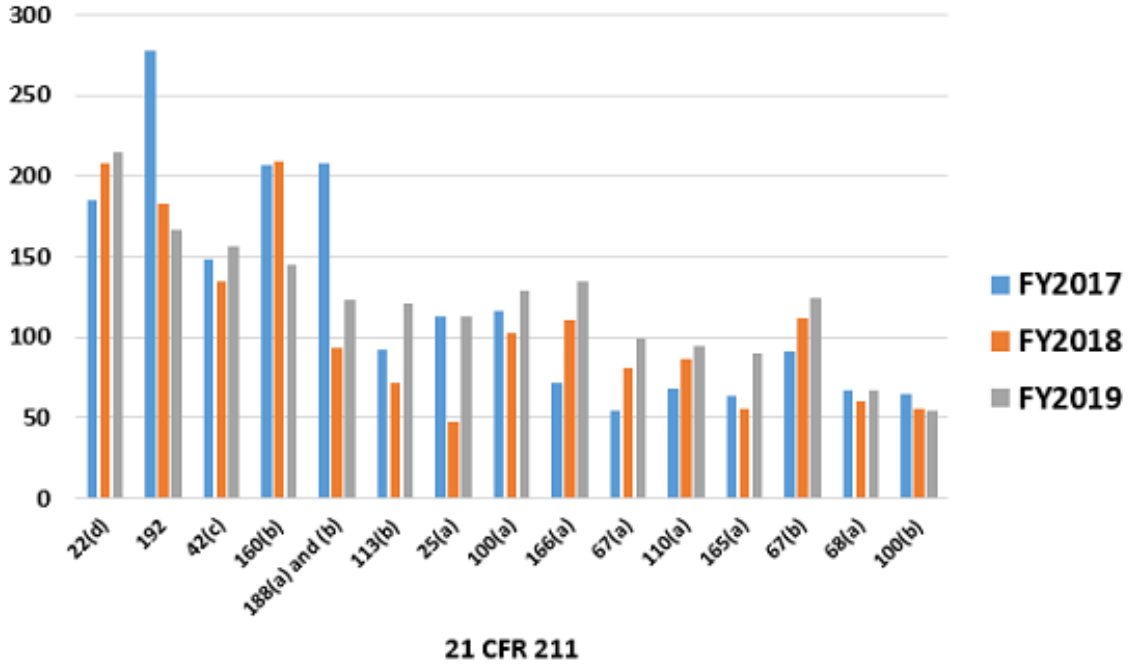
The FDA has already published FY2020 and FY2021 data, however, since the MHRA has yet to do so, the FDA narrow scoped analysis will only be up to 2019. Note, "the FDA's published data only comes from Form 483s issued through its electronic system."[36] It does not represent the FDA's entire library of inspection observations and is approximately a third of the total, meaning the conclusions must be tempered by the relative incomplete nature of the data.[36]

Table 7 presents the top ten FDA observations from 2013-2019 in a condensed form in order of the highest to lowest frequency solely in 2019. Additionally, in the figure is a short description of the Part 211 regulation being cited. There is a great amount of consistency in these numbers with a slight overall increase in both 2018 and 2019. This can also be seen in the total number of FDA Form 483s issued. The bottom five citations are highlighted in grey to signify a greater change in frequency compared to the top five citations. There are several similarities in this table compared to the previous discussion on the MHRA deficiency data. A clear emphasis on the quality control unit can be seen as it has the most citations in 2018 and 2019. Before 2018, the highest cited regulation dealt with investigations of discrepancies (also known as CAPA). There was an emphasis on CAPA throughout the ICH guidelines signifying an effort to harmonize this aspect of the quality unit. Another comparison to the MHRA deficiency data is the increased number of FDA production-related observations. Figure 19 compares the 15 most cited regulations from FY2017-FY2019, throughout these three fiscal years. The increase and decrease of the citation frequencies is very noticeable especially regarding the quality unit and production-related GMPs.

Table 7: Top 10 FDA GMP Inspection Citation Frequency 2013-2019[37]

CITATION	SHORT DESCRIPTION	2013	2014	2015	2016	2017	2018	2019
Total Form 483s issued using FDA tools for Drug Inspections		690	645	678	691	694	716	779
§211.22(d)	Procedures applicable to the quality unit shall be in writing and shall be followed	168	148	165	153	185	208	215
§211.192	Investigations of discrepancies	239	209	250	227	278	183	167
§211.42(c)	Facilities shall include defined areas of sufficient size	94	125	235	227	148	134	156
§211.160(b)	Lab controls should include scientifically sound specifications	199	165	246	133	207	209	145
§211.166(a)	Stability testing	104	82	126	124	72	111	135
§211.100(a)	Production and process controls shall be supported by written procedures	135	107	123	110	116	102	129
§211.67(b)	Equipment cleaning and maintenance	83	80	91	102	91	112	124
§211.188	Master production and control records	114	74	110	100	208	93	123
§211.113(b)	Control of microbiological contamination	119	109	157	118	92	71	121
§211.25(a)	Personnel qualifications	132	115	119	99	113	47	113

Figure 19: Top 15 FDA Citations from F2017-FY2019[37]



CHAPTER 5

THE EFFECTS OF THE COVID-19 PANDEMIC

The COVID-19 pandemic had profound effects on every aspect of human life including drug regulators dealing with these enormous public health challenges. One of the most important and difficult challenges for regulators is how to continue inspecting firms to make certain compliance is being maintained. Both the FDA and MHRA had to adapt to the new pandemic climate to ensure high-quality drugs remained on the market. As seen in Chapter 4, GMP enforcement action data was significantly impacted throughout the pandemic. However, the data wasn't the only aspect affected, the inspection process typically deployed by both the FDA and MHRA had to evolve as well.

The FDA published in May of 2021 the "Resiliency Roadmap for FDA Inspectional Oversight"[38], which outlines the changes in the inspectional process due to the pandemic. In March 2020, the FDA "reserved inspections for mission-critical issues and temporarily postponed all routine domestic and foreign surveillance facility inspections."[38] The FDA determined mission-critical inspections with the following four factors: (1) "products that received breakthrough therapy or advanced therapy designation, (2) products used to treat a serious disease or medical condition and there is no substitute, (3) products requiring follow-up due to recall, there is evidence of serious adverse events, and (4) products related to the FDA's COVID-19 response (e.g. drug shortages)."[38] The FDA conducted 820 mission-critical inspections, with 475 being for medicinal products and 346 being for food.[38] Of the 475 medicinal product inspections, 408 were concerning bioresearch monitoring.

Surveillance inspections were not determined to be mission-critical. However, the FDA created "prioritized domestic inspections" on a situational basis. These situations included a "follow-up inspection on a previous violative inspection, inspections needed to support a product approval decision where no other application deficiencies are known that would preclude approval, and inspections considered high-risk under statutory inspection frequency mandates."[38] Additionally, inspections that maximized the use of limited inspectional resources to achieve the greatest public health impact during the COVID-19 pandemic could be considered "prioritized domestic inspections".[38] The FDA conducted a total of 777 prioritized domestic inspections. Of those, 266 were for medical products.[38]

An additional way the FDA evolved its inspection process outside of mission-critical and prioritized domestic inspection was the use of alternative tools for oversight. The six tools were ways the FDA could optimize its surveillance. The first tool requested the review of records and information in advance of inspections to support regulatory decisions and actions.[38] The second tool applied "remote assessments for individual program areas to evaluate facility records."[38] This tool was critical for evaluating foreign food suppliers. The third tool leveraged information shared by trusted state and territorial regulatory partners to inspect domestic suppliers, again mainly for food.[38] The fourth tool leveraged "information shared by trusted foreign regulatory partners through mutual recognition and confidentiality agreements."[38] This is the most relevant tool with regards to this report as it emphasizes MRAs' increasingly vital work as most foreign travel was suspended. In the explanation of this tool, the FDA specifically references the US-UK MRA. The fifth tool addressed "sampling/analytical testing of FDA-regulated products both domestically and at international borders."[38] Lastly, the FDA refused entry of unsafe imported products into the U.S.[38]

The FDA addressed performing surveillance inspections during the pandemic and recognized most surveillance inspections were postponed. As mentioned in Chapter 2, the FDA plans surveillance inspections by its risk-based approach. Before the pandemic in FY2019, the FDA planned 18,000 inspections and completed 16,920 inspections, with a 94% completion rate. In FY2020 the FDA was only able to achieve a 61% completion rate with 13,000 inspections completed out of 21,000 inspections planned. All 13,000 completed inspections were done before the onset of the pandemic. In FY2021, the FDA planned for 26,250 surveillance inspections which included most of the incomplete inspections from the previous years. As of March 2021, the FDA had inspected 2,953 firms.[39] The FDA acknowledged the help of regulatory partners in both the completed and future inspections, referencing MRAs. It is worth noting that the vast majority of those inspections represent human and animal food facilities. As of March 2021, there were only 3,829 inspections remaining concerning medical products.

Table 8: FDA Inspectional Priority[38]

	Tier 1: Mission Critical	**Tier 2: Higher Priority**	**Tier 3: Lower Priority**
Human and Animal Drugs	• Agency crisis or emergency response activities • For-cause public health emergency work • Essential medicine assignment • Application-approval for high-priority products • Mission-critical violation follow-up	• For-cause but not considered mission critical • Application-approval inspection not considered mission critical • Compounding inspection not considered mission critical	• Post-approval inspection • Routine-surveillance, including inspection and sampling assignment

The FDA is very transparent with the factors that impacted the number of surveillance inspections that were performed in FY2021. It includes the physical availability of investigators, the workload of investigators outside of surveillance inspections, public emergencies,

environmental factors, constraints due to the lifting of COVID-19 restrictions, and the length of time required to plan foreign inspections.[38] Interestingly, the FDA estimated that "25% of the remaining foreign human and animal medical product inspections could be conducted by foreign partners."[38] This emphasizes the growing trust between regulatory agencies and how crucial it has become during a pandemic. After reviewing the complete FY2021 data, the FDA claims to have exceeded its expectations for domestic surveillance inspections. The estimation was calculated by a "Base-Case Scenario" formula which expected the FDA to perform 851 human and animal medical products inspections.[39] The FDA was able to achieve 1,139 inspections, 134% of the estimation.[39]

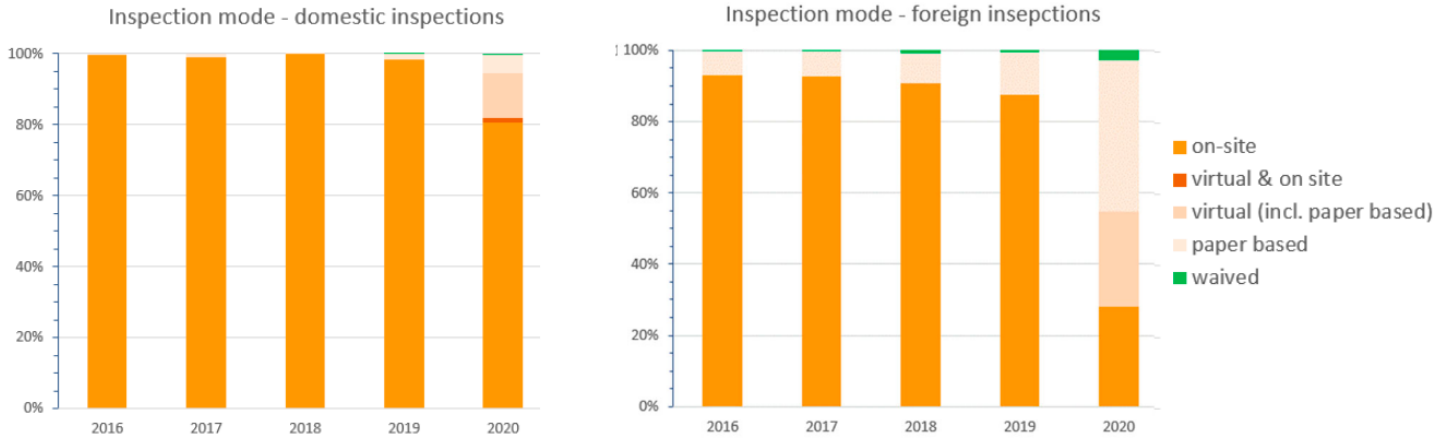
The MHRA has had to adapt to the COVID-19 pandemic. This can be seen by the few guidelines that have been published and updated. The most current one "Guidance for industry on MHRA's expectations for return to United Kingdom on-site inspections"[40] was released in March 2021. The guidance states the on-site UK risk-based GxP inspection program resumed on March 29th, 2021. It will be combined with a remote approach to provide the agency with more flexibility. The guidance does not mention routine inspections and even states "inspections in all settings will usually be pre-notified with minimum 14-day notice to enable COVID-19 risk mitigation planning"[40]. The guideline does define remote inspections as "organizations being asked to provide electronic copies of documents and other information for review off-site, with teleconferences and email to follow up."[41] It also recognizes the importance of PIC/S and MRAs. The table below shows the evolution of FDA and MHRA guidelines published during the COVID-19 pandemic from March 2020 to March 2021. This demonstrates the great efforts both agencies have gone through to adapt to the pandemic environment.

Table 9: FDA-MHRA Remote Inspection Guidelines Published from March 2020-2021[41]

FDA Guidelines	MHRA Guidelines
1. Coronavirus (COVID-19) update: FDA updates on surveillance inspections during COVID-19 (May 2020) 2. Coronavirus (COVID-19) update: FDA prepares for resumption of domestic inspections with new risk assessment system 3. Manufacturing, supply chain, and drug and biological product inspections during COVID-19 public health emergency questions and answers (August 2020) 4. Manufacturing, supply chain, and drug inspections | COVID-19 (January 2021) 5. Remote interactive evaluations of drug manufacturing and bioresearch monitoring facilities during the COVID-19 public health emergency (April 2021)	1. New arrangements for MHRA Good Practice inspections due to coronavirus (COVID-19) (March 2020) 2. MHRA regulatory flexibilities resulting from coronavirus (COVID-19) (April 2020) 3. Guidance for industry on MHRA's expectations for return to United Kingdom on-site inspections (August 2020; updated in March 2021) 4. Innovative licensing and access pathway for medicines (December 2020)

The 2020 EFPIA Inspection Survey does provide some excellent data with regard to the effects of the COVID-19 pandemic. Figure 20 shows the different inspection tools (on-site, virtual & on-site, virtual, and paper-based) utilized in domestic and foreign inspections. As expected, there is a drastic change in 2020 foreign inspections. In 2019, nearly 90% of foreign inspections were considered on-site.[30] In 2020, on-site foreign inspections were approximately 25%, with around 20% virtual and nearly 50% paper-based.[30] There is less of an effect seen in domestic inspections with more than 80% of 2020 inspections having a partial on-site presence.[30]

Figure 20: 2020 EFPIA Survey Inspection Tools, Domestic versus Foreign[30]



Additionally, the 2020 EFPIA survey compares countries' inspection tools directly. Figure 21 shows the 2020 foreign inspection tools. The MHRA is included in the EU category. There is a similar percentage of on-site inspections between the FDA and EU, with both having around 55-60%. One difference is the EU utilizes virtual inspections much more than the FDA and the FDA utilizes paper-based inspections more than virtual. Interestingly, EFPIA states that no agency reported using a hybrid approach in foreign inspections. This is a different approach compared to domestic inspections.

Figure 21: 2020 FDA and EU Use of Tools for Foreign Inspection[30]

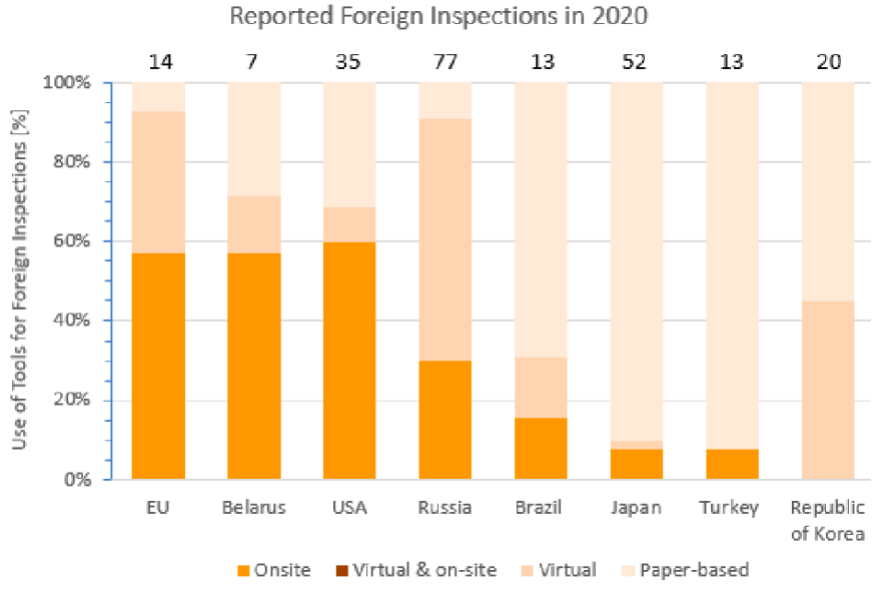
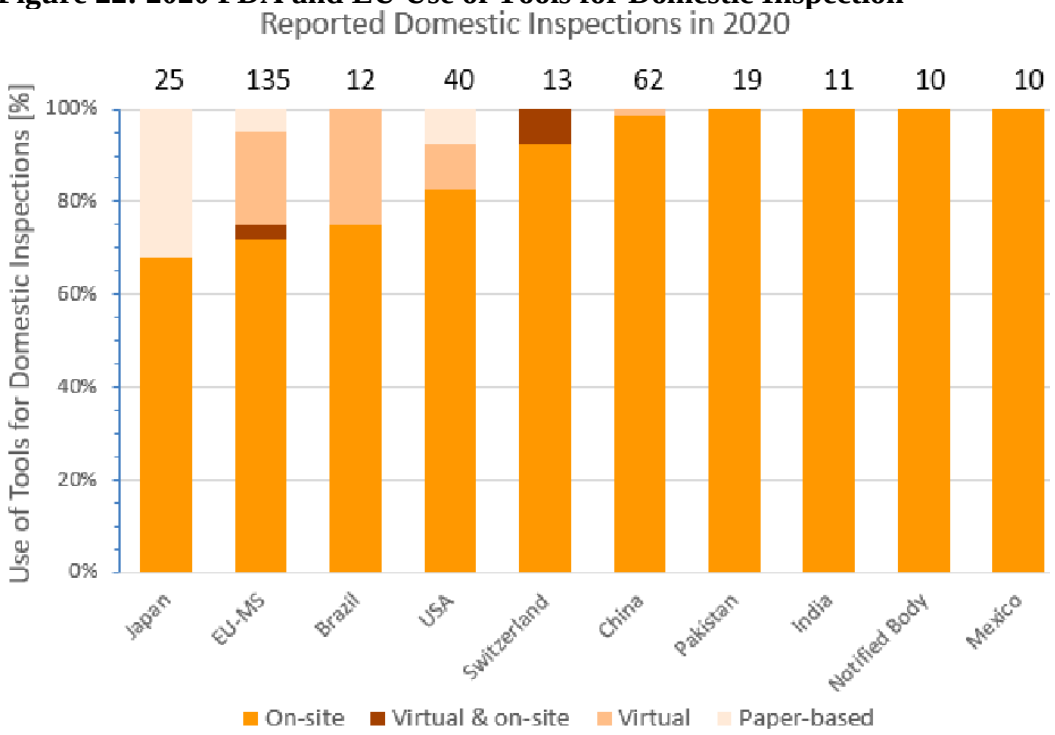


Figure 22 compares countries' inspection tools utilized during 2020 domestic inspections. Again, in this figure, the MHRA is included in the EU category. The FDA does not have any hybrid-based domestic inspections and the EU does. This makes sense as the FDA does not mention the hybrid approach in its Resilience Roadmap publication however, the MHRA does in its guidance for industry. The EU still deployed many more virtual inspections as opposed to paper-based inspections similar to its foreign inspections. However, the FDA seemed to have a more even approach domestically with similar values of virtual versus paper-based inspections.

Figure 22: 2020 FDA and EU Use of Tools for Domestic Inspection[30]



As seen in the updated guidance from both the FDA and MHRA and the clear shift in inspection tools utilized seen in the above data, the COVID-19 pandemic had a dramatic effect on both regulatory agencies. It proves how important managing resources is through harmonization and recognition. The FDA-MHRA MRA and PIC/S positive impact shined during this pandemic and the trust between the agencies continues to build to promote public health.

CHAPTER 6

IMPROVING THE FDA-MHRA MUTUAL RECOGNITION AGREEMENT

Despite the tremendous efforts by industry and the FDA and MHRA, the MRA can be improved by creating an even more efficient global inspection process. Recently, EFPIA published a position paper titled “Opportunities and Challenges with Mutual Recognition Agreement (MRA) on Good Manufacturing Practice (GMP)"[42], that shares the industry's perspective on what can be improved within the current MRA. EFPIA concluded four main points that should be considered to enhance the knowledge sharing and prioritization of resources.[42]

The first point is that the MRA should be fully implemented on all aspects of GMP.[42] That includes both pre- and post-marketing activities in all pharmaceutical products. This would enhance the reallocation of resources as the FDA and MHRA have only recognized surveillance inspections and a limited number of products. Both agencies have several other inspection types that are not covered in the current MRA but are critical to maintaining safe and high-quality products. The second opportunity builds on the previous point. EFPIA believes that the MRA can be optimized to expand the scope of products and activities by updating existing MRAs. EFPIA describes that this can be done by recognizing inspections in 3rd countries, sharing information on quality defects, waiving import testing, and adding devices, biological products, ATMP, and vaccines to the scope.

The third possible opportunity EFPIA sees in enhancing the current MRA is to accept official GMPs documents like EU GMP certificates.[42] EFPIA does hope to see other GMP

documents be accepted in the future. They also state there is room for further harmonization of documents that are submitted. Further harmonization within documentation would provide a more efficient inspection process. Lastly, since EFPIA is specific to the European industry, the final point they state in improving the MRA is to leverage the existing PIC/S documents (i.e. member application procedure and assessment of legislation) to facilitate the assessment of the equivalency of GMP and regulatory oversight by inspectorates.[42] This would aid the FDA and MHRA expand the MRA to other agencies around the world and be able to rely on other agencies for foreign inspections.

The National Academies of Sciences, Engineering, and Medicine published an extensive report titled “Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators"[27] that contains a section on the "improvement of public health through better-designed MRAs". This report has a larger perspective compared to EFPIA as it takes input from “regulatory authorities, international organizations, industry, and patient groups.”[27] The above-mentioned section contains six recommendations. The Committee states “regulations through recognition and reliance arrangements are a 21st-century best regulatory practice since no regulator has the resources it needs to meet all of its public health responsibilities.”[27] They follow by stating the impediments to regulators entering recognition agreements should be removed.[27] The section then describes six challenges that are followed by multiple recommendations for each challenge.

The first challenge is concerning the rapid globalization of the pharmaceutical industry and the overwhelming responsibilities that the regulatory agencies have. The committee recommends “a strategy that leverages the support of each stakeholder group.”[27] They call on all regulatory authorities, especially the well-resourced authorities like the FDA and MHRA, to

"increase information sharing and the transparency of each other's regulatory activities across the product lifecycle."[27] Additionally, they ask for those regulatory authorities to share their work products (i.e. inspection reports, GMP reports) in unredacted forms, especially with those lower-resourced authorities. They state this would enable their access to quality, usable regulatory information to "aid in decision making and reduce the use of limited resources on redundant inspections."[27] It would also "decrease the burden on industry by limiting redundant inspections."[27] The committee asks "lower-resourced authorities to consider the risks and benefits of unilateral recognition of the regulatory decisions of trusted regulatory authorities (both the FDA and MHRA)."[27] Additionally, they ask industry to "support the recognition and reliance efforts of regulatory authorities by encouraging the sharing of less redacted reports with their trusted regulatory authority partners."[27]

The second challenge concerns the EU-US MRA being deployed "under the auspices of trade negotiations, with trade facilitation featuring prominently in the discussions."[27] Instead, the committee wants a shift in focus to improving public health with an emphasis on patients. They recommend policymakers "expand the scope and substance of future MRAs addressing issues related to the safety, efficacy, and manufacturing of quality medicines to ensure that these MRAs are designed, developed, and implemented primarily by regulatory authorities."[27] Interestingly, they add that regulators have to have adequate resources for these tasks.[27]

The next challenge is "responding to evolving science and technology as currently designed MRAs are not sufficiently tools to respond to this rapid pace."[27] The committee recommends an increase in the current scope of MRAs and that "policymakers encourage regulatory authorities to explore opportunities for reliance arrangements with other trusted regulatory authorities."[27] This would allow for "greater flexibility in responding to challenges

that affect their responsibility in overseeing the quality, safety, and efficacy of medicines throughout the lifecycle."[27] The committee specifically describes how the scope could be expanded to "good laboratory practices, good clinical practices, good pharmacovigilance practice inspection reports, and a wider scope of product classes covered by MRAs."[27] This is a repeated theme from both EFPIA and the National Academies of Science Engineering and Medicines. The fourth challenge is similar. That is that even though the EU-US MRA "narrowly applies to areas involving GMP and only to a limited range of products, some of its provisions have still not been implemented."[27] The committee asks both the US and EU (including the U.K.) to immediately implement those provisions regarding so-called "third-country" GMP inspections.[27] Based on the reduction of foreign inspections from the MHRA, it seems some of this has already occurred. However, more time is needed to make any decisive conclusions.

The fifth challenge concerns regulators receiving "incomplete information from other regulators leading to the use of limited resources to needlessly repeat inspections or data assessments."[27] Regulators need complete information for their decision-making. This is similar to the above challenges in that the committee recommends widening the scope of the MRA, asking to "determine whether current limitations on sharing regulatory work products with other regulatory authorities are still fit-for-purpose."[27] This includes the sharing of inspection reports and assessment reports.

The final challenge, which is quite relevant to this report, concerns the evaluation of the effects of MRAs on public health, use of resources, and essential regulatory competencies.[27] There is no "review criteria or framework, including specific metrics, by which regulatory authorities and others can evaluate these impacts."[27] The committee recommends creating a "results framework with clear indicators/metrics and processes for monitoring and measuring the

arrangements' results and impacts."[27] This can be related to regulatory efficiencies, a benefit-risk, or a cost-benefit analysis of the MRA over time.[27] The approach in this report of analyzing GMP enforcement action can only be so reliable, due to the insufficient amount of data. This recommendation would allow for a clear analysis of the effectiveness of the US-MHRA MRA.

CHAPTER 7

FUTURE DIRECTIONS

This report describes a foundation for analyzing the effects of FDA-MHRA MRA. There are several aspects of this report that can be built upon in the future. Of course, any update to the current MRA would be a priority. Several groups are calling for changes to the current agreement. Any potential changes should be analyzed and understood before analyzing the effects of an updated agreement. Furthermore, it is likely the inspection process of both the FDA and MHRA will evolve in the future. This will be another aspect that will have to be reviewed and understood before any analysis of inspection data. The COVID-19 pandemic caused new inspection techniques to be deployed. It will be of interest how remote and paper-based inspections will continue and how the FDA-MHRA MRA will be affected. The same can be said for on-site inspections and how they will evolve in the future with domestic and foreign inspections. There is great potential to save on regulator resources by utilizing these newer inspection processes, which goes hand-in-hand with the purpose of the MRA.

Any future analysis of the effects of the FDA-MHRA MRA will have to include an updated analysis of the GMP enforcement action data. This is contingent on the continued publishing of both agencies' GMP enforcement action data, which is not guaranteed for the future. For an accurate analysis, both agencies will need to continue to be transparent with their inspection data. The MHRA is two years behind the FDA in releasing their GMP deficiency data. Once the MHRA has released these data sets (2020 and 2021), there can be a statistical trending of the two agencies' GMP enforcement action data, which can give a more accurate

representation of the effects of the MRA between the two agencies. It will also be of interest if the two agencies release any sort of framework or metric to evaluate their MRA. This would allow for a direct analysis from the agencies on the effects of the agreement. Additionally, if there is a widening in scope of the MRA in the future, there will have to be a change in the data being analyzed. This includes more products being analyzed and additional regulatory areas outside of GMPs. It is apparent that continued analysis of the entire FDA-MHRA MRA is needed to truly understand the effects on both agencies and public health in general.

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