The US-EU Mutual Recognition Agreement: A Practicum with the FDA Office of Global Regulatory Operations and Policy

Name:

Setting:
Food and Drug Administration (FDA)
Office of International Programs
Office of Global Regulatory Operations and Policy (OGROP or Global Office)

Site Supervisor:

Date of Report:
April 23, 2017
Abstract

My purpose for this practicum was to contribute to FDA’s efforts in establishing international arrangements and policies that aim to improve drug quality and safety on a global scale. I accomplished this by working in FDA’s Office of Global Regulatory Operations and Policy, specifically with the team working on the US-EU Mutual Reliance Initiative (MRI)/Mutual Recognition Agreement (MRA) and the Pharmaceutical Inspection Co-operation Scheme (PICS). My major task was to assist with improving the operations processes of the MRI to prove to the EU that FDA could deliver on its promise to complete the EU Member State capability assessments by the agreed upon date. This was a critical part of the negotiations for the MRA. I accomplished this task by establishing a tool that will assist FDA assessment teams and ratifiers to complete each EU Member State inspectorate (regulatory authority) capability assessment within a 10-week review window. This tool, which had to be approved by the Acting Deputy Commissioner of Global Regulatory Operations and Policy, was an important part of the finalization of the MRA because it conveyed to the EU that FDA is capable of completing the Member State assessments by the agreed upon date.

Update of Aims and Rationale

Pharmaceuticals are a critical element of the health system. They consume a large share of the total spent globally on health, amounting to over $400 billion. They also play a vital role in global development, as they are identified as key inputs to a number of the Millennium Development Goals (Hanson, Palafox, Anderson, & Guzman, 2012). During the past three decades there have been significant changes and trends in the global pharmaceutical industry. U.S. and European firms have long dominated the global pharmaceutical industry; however,
pharmaceutical manufacturing continues to move out of the U.S. and Europe. The fastest growing pharmaceutical manufacturing centers include India, China, Southeast Asia, Korea, Brazil, Middle East and Russia. Furthermore, China and India are expected to account for 80% of global active pharmaceutical ingredient (API) production within the next 10 years (Gren, 2010). This increase in global pharmaceutical manufacturing has led to an increase in substandard medicines. Substandard drugs arise as a result of lack of expertise and infrastructure, inadequate local regulation of the pharmaceutical industry and the lack of good manufacturing practices (GMP) facilities in many developing countries (Newton, Green, & Fernandez, 2010). Of the 190 World Health Organization (WHO) member states, 50% have partially developed regulatory systems and 30% have no drug regulation or a capacity that hardly functions (Hanson, Palafox, Anderson, & Guzman, 2012). When regulatory enforcement is weak or lacking, pharmaceutical manufacturers may ignore regulatory requirements and the quality, safety, and efficacy of medicines may be compromised. Poor quality drugs can cause serious health and safety risks that transcend national boundaries. Poor quality drugs have become a significant global health problem that disproportionately affects people in poor countries (Newton, Green, & Fernandez, 2010). In addition to increased mortality and morbidity, they pose the risk of drug resistance and loss of drug efficacy. Poor quality drugs also cause economic loss for the patient, their families and health systems. Furthermore, they create an increased burden for health care workers, drug regulatory agencies and customs officials (Newton, Green, & Fernandez, 2010). Possible approaches to combating the global problem of substandard drugs include capacity building and workforce training in the technical skills required to establish and maintain effective pharmaceutical regulatory authorities, especially for developing countries. There also needs to be coordination and enforcement of regulatory standards across nations to
ensure safety and quality regardless of where a drug is produced (Hanson, Palafox, Anderson, & Guzman, 2012). Furthermore, the comprehensive inspection of drug manufacturing facilities around the world is critical, and greater emphasis should be placed on facilities in countries that pose a greater risk.

The U.S. Food and Drug Administration (FDA) is committed to international product quality and safety efforts including global collaboration, global data-sharing, development and harmonization of standards, field operations, compliance, and enforcement activities (U.S. Food and Drug Administration, 2016). Although the FDA conducts hundreds of inspections of drug manufacturing facilities outside of the U.S. each year, it is only reaching a small fraction of the registered facilities around the world. As such, the Agency needs to work collaboratively and strategically with trusted partners around the world to ensure that patients in America and around the world have access to safe, effective, and high quality drugs. In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA), which gave FDA the authority to rely upon the inspections conducted by foreign drug inspectorates, once they are found capable of conducting inspections that meet U.S. requirements. This authority (FDASIA Section 712) would allow FDA to shift FDA inspections from countries with well-trained inspectorates to countries that are less established and may pose a higher risk to global health. Building on previous collaborations, the FDA and the European Union (EU) examined where they were conducting foreign inspections of drug manufacturing facilities and determined that a large portion of their foreign inspections were being conducted in each other’s respective territories. Sometimes, the EU and FDA would in the same year, inspect some of the same facilities even if the facilities had a strong record of compliance (U.S. Food and Drug Administration, 2017). In 2014, the U.S. and European Union (EU) regulatory authorities
launched a strategic collaboration—the Mutual Reliance Initiative (MRI), to evaluate each other’s regulatory and procedural frameworks for the inspection of drug manufacturers and to determine the risk and benefits of mutual recognition of drug inspections (U.S. Food and Drug Administration, 2017). The MRI would culminate in an amendment of the 1998 U.S.-EU Mutual Recognition Agreement (MRA). Under this agreement, the FDA will conduct capability assessments of the inspectorates of each of the 28 member states of the EU to determine whether each member state’s inspectorate is capable of conducting facility inspections that meet U.S. requirements. The EU will also assess the capability of the FDA (U.S. Food and Drug Administration, 2017). If a member state’s inspectorate is found ‘capable’ by the U.S., the country’s and U.S. regulators will be able to utilize each other’s good manufacturing practice inspections of pharmaceutical manufacturing facilities. Simply put, EU country inspectors inspect in their respective countries, FDA inspects the manufacturing facilities in the U.S., and the EU and FDA would rely upon each other’s inspection reports (U.S. Food and Drug Administration, 2016). Ultimately, relying on each other's inspections will enable FDA and EU to avoid the duplication of drug inspections, lower inspection costs, and reallocate valuable resources towards inspection of drug manufacturing facilities with potentially higher public health risks across the globe. This will benefit patients and reduce adverse public health outcomes (U.S. Food and Drug Administration, 2017).

My goals for this practicum were to understand and gain an in depth knowledge of FDA’s international product quality and safety efforts including global collaboration, global data-sharing, development and harmonization of standards, field operations, compliance, and enforcement activities. I also planned to gain hands-on experience on the operations aspect of FDA’s Mutual Reliance Initiative and/or the Pharmaceutical Inspection Co-operation Scheme.
My goals remained the same over the course of the practicum. My practicum experience gave me a better appreciation of the magnitude and impact of the issue of poor quality pharmaceuticals in the global market. This practicum was my first exposure to FDA’s international programs and perhaps the most revealing thing to me was the complexity and amount of time and resources involved with negotiating an international agreement. I also realized the importance and impact of the work of established regulatory authorities such as the FDA in combating the issue of poor quality drugs; however, I also realize that a lot still needs to be done because only a small fraction of the facilities that pose the greatest health risk are being reached. The following are examples of what FDA investigators are finding during their international inspections.
As a result of my experience during this practicum, I plan to pursue further work in the area of FDA’s global collaborations to improve the health and safety of the public.
Update of Approach, Methods and Findings

There were several steps involved in meeting the aims of my practicum. I had meetings with my mentor at least once a week and we would discuss a specific topic. After the meetings she would give me follow-up tasks and provide suggested reading materials for the next topic of discussion. To be successful at this practicum, I had to understand the organizational structure and function of the Office of Global Regulatory Operations and Policy and how the Office’s work aligns with the mission of the FDA. Next, I had to research and fully understand the issues surrounding the global manufacturing of drugs that are unsafe, ineffective and of poor quality, including the devastating health consequences of improperly formulated, contaminated or counterfeited drugs to the health of populations around the world. I then had to review findings from the research literature and apply that knowledge to the new vulnerabilities and catastrophic health threats that come with globalization and the increasing interconnectedness of the world. Next, I had to summarize and understand the laws, regulations and administrative provisions governing facility inspections and the GMPs requirements. These included the Federal Food, Drug, and Cosmetic Act, specifically, 21 USC 351(a)(2)(B) (drug adulterated if not manufactured in conformance with current good manufacturing practice); 21 U.S.C. 355(d)(3); 21 U.S.C. 355(j)(4)(A) (approval of human drug contingent on adequacy of methods, facilities, and controls for manufacturing, processing, and packing to preserve the identity, strength, quality, and purity of drug); 21 U.S.C. 360b(c)(2)(A)(i); 360b(d)(1)(C) (approval of animal drug contingent on adequacy of methods, facilities, and controls for manufacturing, processing, and packing to preserve the identity, strength, quality, and purity of drug); 21 U.S.C. 374 (inspection authority); 21 U.S.C. 384(e) (recognition of foreign government inspections). Also of relevance is the Public Health Service Act, specifically, 42 U.S.C. 262(a)(2)(C)(i)(II) (licensing of biologic
contingent on demonstration that the facility in which it is manufactured, processed, packed, or held meets standards designed to assure that the product continues to be safe, pure, and potent); 42 U.S.C. 262(j) (Federal Food, Drug, and Cosmetic Act applies to biologic products); and 21 CFR Part 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding Drugs; General); 21 CFR Part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals); and 21 CFR Part 600, Subpart B (Establishment Standards); Subpart C (Establishment Inspection). The next step was to fully understand the processes involved in the Mutual Reliance Initiative which is the precursor to the Mutual Recognition Agreement. As part of the MRI, FDA had to observe the EU’s Joint Audit Programme, in which two EU nations audit the inspectorate of another member. This unprecedented access allows FDA observers to gather firsthand knowledge of the laws that govern EU GMP drug inspections and how inspectorates manage the drug inventory within their respective borders. Also, interacting with auditors across the EU provides a unique opportunity to understand the regulatory framework in the EU. With 28 member states (27 after Britain leaves the EU), there can be differences FDA must understand. FDA first observed the audit of Sweden’s inspectorate by auditors from the United Kingdom and Norway. To date, FDA has observed 13 drug inspectorates across the EU with more audit observations planned through 2017. The end goal of the MRI was that it would lead to the signing of the MRA between EU and FDA. The MRA is the agreement that outlines how the EU will assess the FDA, as well as the process and timeline for how the FDA would use the information gathered during the MRI observations to make an EU member state inspectorate capability determination. There is a clause in the MRA that requires the FDA to complete all 28 member state capability assessments by July 15, 2019. During negotiations and prior to the signing of the MRA, the FDA had to prove to the EU that it will be able to keep its end of the
bargain. This is where my practicum project is relevant. As stated earlier in this report, I was tasked with establishing a tool that will assist FDA assessment teams and ratifiers to complete each EU Member State inspectorate (regulatory authority) capability assessment within a 10-week review window. This tool was critical in the final negotiations of the MRA. Once I fully understood the background of the MRA and the significance of my project in the finalization of the MRA, it was time to start developing the tool. I had to understand the key players involved in the member state assessments and their roles at each step of the assessment. The key players include the primary assessment team, the secondary assessment team and the ratifiers. The primary assessment team includes FDA inspectors that were involved in the Joint Audit Programme observations and other FDA staff. They review the inspectorate audit report and other prerequisite materials and they provide their findings to the secondary assessment team. The secondary assessment team is made up of experts from several FDA Centers. They review the findings from the primary assessment team and verify that the assessment process was followed, ensure consistent interpretation among primary assessment teams and they make a recommendation of capability to the ratifiers and note any limitations. The ratifiers include Center director level staff and they make the ultimate determination of capability. The tool had to ensure that each capability assessment could be complete in 10 weeks, which is quite ambitious given the substantial amount of information that needs to be reviewed and the difficulty in getting staff from different FDA Offices to meet on a regular basis. After several meetings with the Office of Global Regulatory Policy project management team and FDA’s Associate Commissioner for Global Regulatory Policy and 6 drafts of the document, I was able to finalize a tool that the Associate commissioner approved. Unfortunately, this tool is considered an internal FDA document so I am unable to include it in this report. In addition to my major project, I was
assigned other collateral tasks related to the MRA. I think I had a good approach to my practicum and I don’t think I would do things differently if I were to do it again. As a result of my work, the FDA is able to prove that it is capable of completing all 28 member state capability assessments by the date set forth in the agreement. This was an integral part of the negotiations for the MRA.

**Reflection on the Practicum**

This was an extremely rewarding experience for me. I have always had an interest in FDA’s global regulatory work, but I’ve been hesitant to seek a position in the field because I don’t have any global regulatory experience and I also wanted to be sure that the Global Office would be a place I would enjoy working in. This practicum was the perfect avenue for me to gain some experience in the global field as well as get a sense of the work culture in the Global Office, while still keeping my current position. I have nothing but positive things to say about my experience. My site supervisor was very accessible and was genuinely interested in making sure I learned as much about the Office as I could. She introduced me to the rest of the project management staff that I would be working with and everyone was very welcoming. She also introduced me to FDA’s Associate Commissioner for Global Regulatory Policy, Dara Corrigan. The highlight of my experience was when during a meeting, Dara Corrigan paused to make sure I understood the importance of my project and that she appreciated my work with the team. The main challenge I faced during the practicum was the time commitment required. This practicum required a lot of reading and research on my part. I had to keep up with my regular job, two other MPH courses and family responsibilities, in addition to the work I was doing with the practicum. What kept me going was the fact that I really enjoyed what I was learning and I was excited to be playing a role, no matter how small, in the furtherance of global pharmaceutical quality. What
surprised me the most was the impact of the new presidential administration on the MRA. With the inauguration of the new president came many uncertainties and many Global Office staff were nervous about the future of the MRA. Thankfully, the agreement was finalized successfully. This practicum has given me the opportunity to gain experience in the field of global regulation of pharmaceutical quality which will be helpful for my career.

Conclusion

During this practicum, I was able to explore my interest in global health as it pertains to ensuring greater coordination and enforcement of regulatory standards across nations to ensure safety and quality regardless of where a product is produced. Through my work with the MRI/MRA, I had an opportunity to contribute to FDA’s efforts in ensuring that global health is protected and advanced. I had an appreciation for the complexity of negotiating a mutual recognition agreement and the amount of time and resources involved with negotiating an international agreement. I also realized that while the FDA is doing its best to inspect foreign facilities, it is impossible to reach the majority of the facilities that pose the greatest risk to public health, hence the need for strategic collaborations with trusted partners. Finally, I realized that the quality of a practicum experience depends greatly on the quality of mentorship of the site supervisor and I am very grateful that I had a committed site supervisor.
Bibliography


