

STUDII

**A PRESCRIPTION DRUG PRIORITY FOR THE EUROPEAN MEDICAL AGENCY POST
BREXIT: OVERSIGHT OF MARKET-APPROVED MEDICATIONS¹**

DOI:10.24193/SUBBiur.62(2017).3.2

Published Online: 2017-09-30

Published Print: 2017-09-30

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Motto: *“Orgoliul unui om născut într-o cultură mică este întodeauna rănit”*
“The dignity of a man born in a small culture is always wounded”
“La dignité d'un homme né dans une petite culture est toujours blessée”
Emil Cioran

Abstract: *The United Kingdom’s BREXIT decision on June 23, 2016 triggered a movement to relocate the European Medical Agency (EMA)—the EU’s market gatekeeper and overseer entrusted with the mission to ensure the safety and efficacy of prescription medications—from its London base. Several EU countries have begun vying to become the new home of the EMA, and existing skilled and experienced EMA staff are relocating and leaving positions that linger as unfilled. The biopharmaceutical sectors and enormous related professional infrastructure that towers over the EMA, anchored in London from its beginning, now stands on shifting soil. Among the enormous EU human health and economic implications, this paper focuses on an immediate concern: ensuring no disruption of ongoing regulatory oversight of prescription medications available to patients across Europe for treatment with EMA assurances of safety and efficacy. This paper proposes that the EU prioritize and implement regulatory reform measures to protect this particular mission and function of the EMA during the Agency’s state of post-BREXIT transition. The paper proposes that pharmacovigilance is distinguishable and should be prioritized given the ongoing reliance of health care providers and their patients on these products under the regulatory assurances of safety, efficacy, and ongoing oversight that have made them available for treatment use. The paper introduces a law and policy proposal to accomplish this goal.*

Key words: *Health Law, Comparative Health Law, European Medical Agency, Market Gatekeeper, BREXIT, Pharmacovigilance, Public Health, Biotechnology, Genomics Revolution, Centralized Procedure, EU Law, Directives, Regulation, Food and Drug Administration (FDA).*

Cuvinte cheie: *Drept Medical, Drept Medical Comparat, Agenția Europeană pentru Medicamente, BREXIT, Farmacovigilență, Sănătate Publică, Biotehnologie, Revoluția Genomică, Procedura Centralizată, Dreptul UE, Directive, Regulamente, Agenția pentru Alimente și Medicamente.*

"Fluctuant nec mergitur"
"Tossed by the waves but never sunk"

I. Introduction

The European Medical Agency ("EMA") is the gatekeeper to one of the biggest and most profitable biopharmaceuticals markets in the world, the European Union ("EU") biopharmaceutical market.² The United States of America, EU and Japan constitutes the world's three largest biopharmaceutical markets.³

However, the role as market gatekeeper is not just to decide if products are suitable to enter the EU markets, but also to stand over them once they are there.⁴ The dual role is to ensure the safety and efficacy for products deemed market worthy and to oversee the same thereafter through ongoing market oversight and supervision.⁵ The focus of this EMA function is patients with health care needs taking medications with assurances and the physicians caring for them. The importance of this section function has escalated in an age of genomics complexity and the market introduction of innovative new products, many for life-threatening or otherwise seriously debilitating health conditions without sufficient treatments.⁶ In addition, EMA's role is to coordinate the Member States pharmacovigilance activities and to ensure rapid recall from the market once they are presenting a negative risk-benefit balance under normal conditions of use, in accordance with EU Regulation 726/2004 of the European Parliament and of the Council, O.J. L. 136 (2004).

The human health significance of the EMA's post-authorization function is exemplified by its actions. A notable recent example is the EMA's August 2014 recommendation that the drug Vistide be removed from the market.⁷ The EMA had recommended Vistide for market use to treat cytomegalovirus ("CMV") retinitis, a viral infection of the retina (the light sensitive surface at the back of the eye), in 1997.⁸ The EMA, had recommended the marketing authorization on the European market through its centralized procedure.⁹ The Committee for Medicinal Products for Human Use ("CHMP") determined that Vistide's benefits were greater than its risks for the treatment of CMV retinitis in patients with AIDS and without kidney disease. The European Commission ("EC") followed the EMA's recommendation and granted authorization.¹⁰ However, in 2013, at which time Vistide was being distributed in all EU Member States ("MSs"), the market authorization holder notified the EMA with a voluntary product recall due to manufacturing challenges, as well as a decreasing incidence of CMV retinitis in adults with AIDS.¹¹ The EMA issued a recommendation to the EC to recall Vistide from the market, and the EC issued a decision to do the same on August 22, 2014.¹²

The EMA's November 2016 recall of allogeneic umbilical cord blood cells ex vivo for the treatment of Acute myeloid leukemia ("AML") provides another recent illustration of the Agency exercising and meeting its pharmacovigilance responsibilities.¹³ This example, a biologic (derived from living organisms) human health product, is particularly significant given it represents the forefront of biopharmaceutical research and development, the genomics revolution.¹⁴ This revolution, generally associated with the Human Genome Project, is challenging regulators with exponentially escalated scientific complexities.¹⁵

The EMA had recommended approval of allogeneic umbilical cord blood cells *ex vivo* for market use to treat Acute myeloid leukemia (“AML”), in 2011.¹⁶ Consistent with Vistide, the EMA made this recommendation through the centralized procedure. The Committee for Orphan Medicinal Products of (“COMP”) adopted a positive opinion on 9 February 2011, pursuant to which it recommended orphan designation for Allogeneic umbilical cord blood cells.¹⁷ AML, is a cancer of the white blood cells (cells that fight against infections), is a life-threatening disease.¹⁸ These abnormal immature cells take the place of the normal white blood cells, and thereby reduce the patient’s ability to fight infections.¹⁹ The EC implemented EMA’s recommendation and granted authorization to the market holder.²⁰ However, it did not last long enough because the EMA had to recall it in November 2016 on request of the market holder and without providing further public information.²¹

This paper will focus more on the centralized procedure, given the fact that all the major recalls that can affect the market’s framework are captioned by this procedure.²² Even though the gross majority of the medicines authorized in the EU do not fall within the scope of the centralized procedure but are authorized by national competent authorities (“NCA”) in the MSs.²³

The pharmacovigilance responsibility is an ominous task for the EMA given the fact that the Agency is a blanket over Europe, somewhat analogous to the role of the FDA in the U.S. market.²⁴ Many people waiting for reviews and approvals for potential new treatments for seriously life-debilitation and even life-jeopardizing health conditions would argue that review and approval timeliness is as important for them. This author agrees with the affirmation.²⁵ However, there is reliance on drugs once approved for the market.²⁶

Sometimes, medical products more mainstream though for less dire conditions, such as Vioxx²⁷ (for example to treat arthritis pain with ibuprofen),²⁸ are unquestionably more crushing on a public health level.²⁹ Vioxx had existing treatment substitutes that after the United States put it on the market, and were found as effective in the vast majority of patient cases.³⁰ Incidentally, Vioxx was not picked up in Europe.³¹ Therefore, the EMA needed to simply release a press statement following its worldwide withdrawal.³² In contrast, the FDA undertook a major market recall six years after it issued its approval³³-- after thousands of patients paid ten times more for Vioxx than ibuprofen and suffered the side effects of stroke and heart attacks.³⁴

This paper addresses the role of the EMA in supervising and standing guard over the medical products that it approves for the European market—a function known as pharmacovigilance.³⁵ Part I of this paper will profile the EMA’s origins and operations with a focus on the agency’s responsibilities as market gatekeeper post authorization. Specifically, Part I will define the EMA’s pharmacovigilance responsibilities and experience meeting them.

Part II will profile the BREXIT decision and its impact on the EMA, both actual and potential, with a focus on the EMA’s pharmacovigilance responsibilities and their human health significance. The message emphasized in Part II is that the BREXIT decision threatens the pharmacovigilance function of the EMA, which poses an immediate threat to the human health of patients and providers relying on EMA approved prescription drugs and the associated immediate human health implications.

Part III will propose law and policy reforms to secure this EMA function and related human health during the EMA’s BREXIT transition.

II. BACKGROUND: THE EMA'S GENESIS AND PHARMACOVIGILANCE

The EMA was set up to harmonize the work of existing national medicine regulatory bodies and is the EU's body responsible for coordinating the existing scientific resources put at its disposal by MSs for the evaluation, supervision and pharmacovigilance of medicinal products.³⁶

From its genesis in 1995, the EMA has developed into a complex and unique regulatory system for the medical products and medical devices on the EU market, alongside the EC and the MSs Authorities, creating different paths for entering the market and many innovative possibilities to oversee the products they authorize.³⁷ As Professor Malinowski said in its preface of the *Biotechnology Handbook*, "this dynamic environment is a Herculean undertaking."³⁸ The staggering infusion of technology on a sea of constant change demands the need of constant change and adaptation to the new technology and the fact the EMA did not hesitate so far to learn from its mistakes and tried each time to improve them.³⁹

The following discussion first profiles the EMA—its origins, legal foundations, and crystallization of its authority and responsibilities under the law to ensure pharmacovigilance⁴⁰. Subsection B provides a brief assessment of the EMA's success in meeting this responsibility leading up to BREXIT.

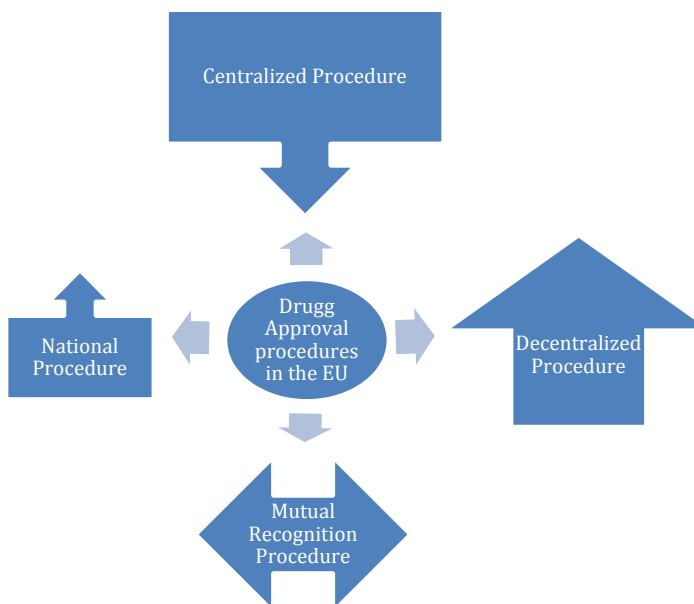
A. The EMA's Law Origins and Fundamentals

The EMA's market authorization and supervision authorities were established when the EMA itself was put in place in 1st of January 1995, as Article 66 says, of the Council Regulation⁴¹ (EEC) No. 2309/93, of 22 July 1993, O.J. (L214), amended and replaced by the Regulation (EC) No. 726/2004.⁴² Its primary task, as described by the original Regulation (No. 2309/93) is to "provide scientific advice of the highest possible quality to the Community institutions and the MSs for the exercise of the powers conferred upon them by Community legislation in the field of medicinal products in relation to the authorization and supervision of medicinal products." This scope is reiterated in the Article 1 of the newly amended Regulation (No. 726/2004),⁴³ but in a more specific manor. The new regulation states that, "the purpose of this Regulation is to lay down Community procedures for the authorization, supervision and pharmacovigilance of medicinal products". In administrative law terms, the EMA is a decentralized agency, which means that the EU as a legal entity delegated its authority powers to the EMA to regulate and supervise the market, making the EMA the gatekeeper for the designated human health products.⁴⁴

US's counterpart to the EMA, the FDA, is responsible for the regulation of a cumbersome portfolio of human health products.⁴⁵ The scope of the FDA's regulatory authority is very broad.⁴⁶ As the EMA, the FDA is also responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.⁴⁷ Most important for

the purposes of this paper, the FDA like the EMA is responsible for ongoing oversight—pharmacovigilance.⁴⁸ In addition, besides the general responsibility of evaluation, supervision and pharmacovigilance of medicinal products.⁴⁹ The Regulation unfolds many other particular tasks into the Agency’s jurisdiction,⁵⁰ one of which enables the Agency to create a complexed and effective regulatory system for medicines. The EMA’s regulatory system is based on a network of around fifty regulatory authorities from the thirty-one EEA countries (twenty-eight EU MSs plus Iceland, Liechtenstein and Norway), the EC and the EMA. This network is what makes the EU regulatory system unique.⁵¹

In order to achieve legislative harmonization and coordination of nationals for biotechnology and other high-tech products, this network (of national experts) worked together and created the European authorization system, through the EMA, by implementing defined avenues for such an authorization to take place. The main ones are the centralized,⁵² decentralized⁵³ and mutual-recognition⁵⁴ procedures.⁵⁵ In addition, on the EU market most of the medical products authorized by the Agency are *via* the centralized procedure.⁵⁶



(Fig. 1)

Once the scientific assessment is granted to the market holder by the EMA, the EC role comes into play, by formalizing the EMA’s decision with an authorization.⁵⁷ Alternatively, the EC may refuse, change or suspend market authorizations in response to the EMA’s initiative.⁵⁸ All of this based on Article 6 paragraph four, Article 9 paragraph three, Article 10 and Article 81 of the No. 726/2004 Regulation.

After all the process of granting a market authorization to a medical product or medical device, from limited market access for clinical research to full market access.⁵⁹ The EMA plays a key role in the safety monitoring of medicines in the EU - known as pharmacovigilance.⁶⁰ The Agency's main role in this area is to support the coordination of the European pharmacovigilance system and to provide advice on the safe and effective use of medicines.⁶¹

The pharmacovigilance legislation has been subject to turmoil over the past decades. "In the early 2000 in response to a crushing adverse drug reactions ("ADRs") that caused around 197,000 deaths per year in the EU."⁶² Prompted the EU Institutions, EU Parliament and Council of Ministers, to take adopt a new Regulation (EU) No. 1235/2010⁶³ and a new Directive 2010/84/EU⁶⁴ in 2010. However, even after the new wave of fresh legislation the arising problems on the EU market could not be stopped, especially in France,⁶⁵ where the Benfluorex⁶⁶ drug kept the first pages of the newspapers for a long time following its recall from the market by the EMA in 2010.⁶⁷ Thus, in 2012 the pharmacovigilance legislation was further more amended with the Regulation (EU) No 1027/2012 and the Directive 2012/26/EU aiming to further strengthen the protection of patient health by allowing prompt notification and assessment of safety issues.⁶⁸

B. The EMA's Pharmacovigilance Assessments

Under EU law, pharmacovigilance activities constitutes the protection and promotion of public health through prevent of harm caused by medicines as well as to enable the safe and effective use of medicines.⁶⁹ Furthermore, based on Article 24 of the Regulation (EC) No. 726/2004 "the Agency shall in collaboration with the MSs and the EC, set up and maintain a database and data processing network (Eudravigilance database)⁷⁰ to collate pharmacovigilance information regarding medicinal products authorized in the Union and to allow competent authorities to access that information simultaneously and to share it."

The EMA mandates the Pharmacovigilance Risk Assessment Committee ("PRAC") to accomplish this mission.⁷¹ PRAC covers all aspects of the risk management, including the detection, assessment, minimization and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorization safety studies and pharmacovigilance audit.⁷² Furthermore, the EMA implemented the Good Pharmacovigilance Practices ("GVP"), which are a set of measures set up to facilitate the performance of pharmacovigilance in the EU, based on Article 108a of Directive 2001/83/EC.⁷³ The GVP covers both the centralized and decentralized authorization procedures.⁷⁴

Reliable pharmacovigilance demands that both PRAC and GVP cover and challenge to meet them, has been and will continue to be exacerbated by the infusion of increasing complexity due to uptake of the genomics revolution in drug research and development.⁷⁵

There is no doubt that the genomic era medical products tend to be much more potent, with a much higher level of metabolic impact, in other words, the sophistication and complexity of this generation of drugs necessitate heightened scrutiny by their very

nature⁷⁶ and even the oversight has to be distinct from the less comprehensive (pharmaceutical) medical product.⁷⁷ Genomics has just heightened the pharmacovigilance challenge with the thrust of the genomics revolution only intensifying in drug development. Furthermore, both the U.S. and EU now that they have recognized new classes of biopharmaceuticals,⁷⁸ biosimilars⁷⁹ and interchangeables,⁸⁰ which makes the mission yet more difficult.⁸¹ Cousins to generic drugs, they were introduced to accelerate access and bring down costs; these too are much more complicated to regulate, due to their complexity, in the market than their traditional medical counterparts.⁸²

As a pharmacovigilance assessment example, there were 201 generic medical products (not biosimilar) authorized by the EMA from which only twenty-five were withdrawn from the market between 2009 and 2016.⁸³ Whereas the biosimilar medical products list is reduced, EMA authorized only twenty-five from which only two were withdrawn, like Valtropin and Biogastim whereas Filgastim Hexal was withdrawn in 2008 and authorized again in 2009.⁸⁴ So we can see a cautious and exertions endeavor from the Agency's part when it comes to a generation of medical products that are the technology crest on the RX (Prescription drugs) pipeline.⁸⁵

Furthermore, since 2014, companies have been required to report the cessation of marketing of a medicine in any MSs for reasons affecting patient safety so that the authorities can ensure that the same action is taken across all MSs. In addition, the EMA is responsible for the coordination of these actions across the EU. In 2015, the EMA received 160 notifications of withdrawn products, compared to 132 in 2014.⁸⁶ Furthermore, manufacturers are required to inform authorities of quality defects in batches of a manufactured product, which can lead to a recall of batches from the market, or prevention of their release by the manufacturer.⁸⁷ The number of quality defects fluctuated since 2011, with a top of 178 quality defects in 2013 and 164 in 2015.⁸⁸

C. The Legal Consequences of the BREXIT Decision – Short Overview of Article 50 of TEU

The summer of 2016, might be deemed the *bête noire* of the European Union.⁸⁹ The unprecedented⁹⁰ happened and by a general suffrage, a majority of the U.K. population voted against continuing the membership to the EU⁹¹ and since its formation,⁹² the EU, UK⁹³ can be the first country that chooses to leave by using its right to withdrawn from the Union profiled in Article 50 Treaty on EU ("TEU"), also known as the Lisbon Treaty.⁹⁴

The right to withdraw is embedded in Article 50 TEU based on international customary law.⁹⁵ Also, "prior to the Lisbon Treaty t was no provision in the Treaties addressing secession of a member state. The Community and Union Treaties did not; rather, they were concluded for an unlimited period and silent on the matter of withdrawal of a MSs."⁹⁶ Nevertheless, EU MSs founders chose to retain the possibility of withdrawal without recourse under international law since EU choose to govern its own procedure and consequences of withdrawal no recourse to the international law is possible.⁹⁷ The article is criticized because it does not

stipulate any formal reason requiring the Member State to provide when chooses to use its right of withdrawal⁹⁸ and the rescission procedure unlike the accession of a Member State is furthermore complicated.⁹⁹

UK's exodus atop a progressive movement that is shaking both US and EU governments is ominous in that it is challenging the seams of unity that have held the EU market together for decades, and which the governments and citizens of the EU have come to rely on.

III. THE BREXIT EXODUS: A THREAT TO PHARMACOVIGILANCE RELIABILITY

The BREXIT decision has posed an immediate threat to EU's pharmacovigilance function.¹⁰⁰ The EMA's dependence on that function is umbilical tied with its very core and the necessity of no disruption, especially in an age of infusion of technology and complexity can pose a crucial threat for the EU public health.¹⁰¹ The decision has cracked the foundation of the long-established London location and made a shift in location almost a certainty. Also caused disarray to the very operations of the EMA. The reliability of ongoing pharmacovigilance for the patients taking and physicians administering biopharmaceuticals already is becoming as uncertain as the EMA's future location, is not known for now. Although the implications of the BREXIT decision on the EMA and the future of human health throughout Europe are immense,¹⁰² the impact on the reliability of ongoing pharmacovigilance, patients taking medications and physicians prescribing them, innately demands immediate attention.

There is much to learn from the EMA's homologous across the Atlantic, the U.S. FDA, and the need for Europe to have a mechanism for immediate and automatic uptake such as the FDA does,¹⁰³ especially in biologics through its Center for Biologics Evaluation and Research ("CBER").¹⁰⁴ Although there is established ongoing reliance also that, the EMA is a decentralized government entity,¹⁰⁵ especially when compared with the U.S.'s FDA market gatekeeper (in its function and the fact that each health system makes independent decisions about uptake of the EMA-approved medications).¹⁰⁶

The EMA has established itself as the orchestrating, overseeing government entity regarding what biopharmaceuticals are safe and efficacious.¹⁰⁷ The concentration of pharmacovigilance, decision-making, and the professional and scientific expertise to make those decisions, in London has been put in jeopardy.¹⁰⁸ This is evident by the already documented exodus of needed staff and scientific expertise from London, diffusion of that in other EU locations, and the shattering of focus.¹⁰⁹ The pharmacovigilance function is crucial for the EU market because the impact - and potential further impact - is on products, the patients are taking and providers are prescribing. Which can cause a major public health care problem.¹¹⁰

A. EMA's Infrastructure and Its Potential Disruption

"Located in London's Canary Wharf, with around 900 highly skilled staff, the EMA serves a market of over 500 million people across the EU, accounting for twenty-five per cent of all global pharmaceutical sales. On its own, the UK accounts for just three per cent."¹¹¹

The EMA has succeeded from its base in London in pursuing its tasks and responsibilities. “[The Agency] relied heavily on the collaboration with its partners in the EU regulatory network and its scientific resources”¹¹² in order to consolidate and coordinate such a complex and fragile infrastructure over the past twenty years.¹¹³

“The Agency's remit has expanded over time, in line with new EU legislation.”¹¹⁴ Moreover, with the creation of the PRAC in 2012,¹¹⁵ EMA started to play an even more important role in monitoring the safety of medicines across Europe.¹¹⁶ “The synergistic efforts of the network of national regulatory agencies of the EU, with the key role of the European Risk Management Strategy group, and under the coordination of the EMA, have been crystallized in a unique system of trust and collaboration aimed at protecting public health.”¹¹⁷

With a total revenue in 2015 of €304.119 million, representing a twelve per cent increase compared to 2014 (€271.786 million).¹¹⁸ This increase is mainly due to the implementation of the pharmacovigilance fee regulation in August 2014.¹¹⁹ In addition, the total number of Agency staff as of December 2015 was 890 (623 women, 267 men).¹²⁰ The EMA regulatory network, gives the Agency access to a pool of over 4,500 experts, allowing it to source the best available scientific expertise for the regulation of medicines in the EU.¹²¹ Which provides a great income and job opportunities for the country that hosts the Agency.

A big and arising issue for the EMA after the BREXIT vote is the fear of staff exodus.¹²² The head of the EU's London-based drugs regulator, Guido Raisi, said “the agency had lost an unprecedented number of senior staff since the BREXIT vote and warned that as many as half could walk out unless its future is handled properly.”¹²³ He furthermore specified, “Seven senior executives had quit the agency since the referendum, more than in the past decade put together”.¹²⁴ Also, “[a] staff survey presented to the agency's governing board last week showed that about 50 per cent would leave in the event of relocation to an undesirable city.”¹²⁵

In addition, the big pharmaceutical companies following the BREXIT vote announce big disruptions. U.K. Big Pharma CEO, Sir Andrew Witty warned of “tremendous disruption” if the EMA would move from its base in London.¹²⁶ Sir Andrew's concern is “that moving the EMA and its 900 staff members from London to another European city post-Brexit will cause upheaval that affects the smooth running of the regulatory machinery.”¹²⁷ Martin Munte, president of the Austrian Pharmaceutical Industry Association in Vienna, said that moving the Agency is a “Herculean task” and an early decision could help to keep disruptions to a minimum.¹²⁸ In addition, “Japanese officials told their U.K. counterparts that if the EMA leaves London, the R&D budgets of biopharma companies might follow the regulator.”¹²⁹ Also, “[w]hen the U.K. government tallied up the country's biggest investors in biopharma R&D in 2010, Eisai was the only Japanese drug maker near the top of the pile.”¹³⁰ This warning profiled could be a good indication that U.K.'s risks losing what is left of its non-native biopharma R&D sector are rising.¹³¹

Even though the EMA was successful in coordinating and culminating the needed scientific expertise and it actually released an official statement saying, “its procedures and work streams are not affected by the outcome of the referendum”.¹³² With the RX

(prescription drugs) research and development trend is to be much heightened and rising in scientific expertise and complexity.¹³³ EMA's CEO fears that "[w]ithout a proper amount of time — a minimum of two years — the approval of drugs in the EU could suffer and recent improvements in approval times¹³⁴ could stall or even go into reverse, leaving Europe's burgeoning biotech sector to seek approval in the US or Japan or in future in Korea or Singapore."¹³⁵

The practical impact of the BREXIT decision can be a disruption both in approvals¹³⁶ and disruption in public health readiness—e.g., effectiveness in monitoring the human health products. Also can be a potential threat to the EMA pharmacovigilance function with all the increasing number of withdrawal and recalls in the recent years and with the infusion of technology, which need heightened scrutiny. All this concerned is shared by the head of the EMA Mr. Raisi which says "Imagine if we are late in reaction for some crisis, something going wrong, something unexpected, some quality issue," he added. "If we are not in a position to intervene fast and efficiently," he added, "that is a serious threat to public health."¹³⁷ Also, Mr. Zeichner, whose Cambridge constituency has a large life sciences sector, "fears that Brexit could increase the cost of drug authorizations and slow access to new medicines for Britons."¹³⁸

B. The Overall Impeding Effect of BREXIT on the EMA as a Regulatory Body and its Potential New Home

The diffusion of the concentration of scientific expertise within the EMA, at the London base, complemented by the professional services and industry infrastructure established with that location focus has been built up over the past twenty years and made the complex regulatory network it is today. Therefore, "a new site should [not] be amenable to relocation of 890 highly skilled staff members and their families to maximize retention of the existing workforce."¹³⁹

"While the European macroeconomic outlook is quite gloomy, the pharmaceutical industry is set to grow at a sustained rate through 2022, exhibiting 3.2% growth during the 2015-2022 timeframe.", this is an Evaluation conducted by the European Drug Forecasts, June 2016.¹⁴⁰ Evaluation that makes the pharmaceutical sector, a big contributor to the EU's trading and commercial power.¹⁴¹ Furthermore, the EMA seems to be appealing enough for other EU countries to make lobby in order to get the Agency post-BREXIT.

There are already EU countries vying to be the future host of the EMA. The UK vied for the EMA in negotiations that made UK a MS to the EU, thus it is no surprise that several MSs are vying just as hard, if not harder now to become the EMA's new home. One of the benefits is to establish a biopharmaceutical epicenter in their borders and to reap all the infrastructure benefits that the UK has enjoyed, with the potential of scientific and professional expertise to boost their own biopharmaceutical sectors and advance their own scientific technology. Without any doubt, acquiring the EMA headquarters will be a political and regulatory coup for whichever country succeeds. "The successful candidacy is

likely to significantly raise the investment profile of the host country in the pharmaceutical and life science sectors.¹⁴² Making the host country the epicenter of the EU's pharmaceutical market process.

More than a dozen countries had expressed an interest in hosting the EMA after it leaves the UK, cities like Milan, Brussels, Copenhagen, Dublin, Lille, Stockholm and Warsaw are in the race.¹⁴³ "There is also hope, however distant, to keep the agency in the U.K., too: No law explicitly states the agency cannot sit outside the union and London has a solid case."¹⁴⁴ This fray for becoming the EMA's new home is complemented by movements to both maintain the London presence and another to move the EMA to one of the EMA's newer members Croatia or even Bulgaria. The latter is supported by the same considerations that are fueling competition to claim the EMA—to fuel scientific capabilities and their biopharmaceutical capabilities, both in the science and in complementary professional services. However, "experience shows that agencies located in very remote places face severe difficulties to attract and retain staff from the rest of Europe."¹⁴⁵ In addition, "[t]o be in contention, countries will need to generate political support at an EU level, and this process will tend to favor the larger EU countries over smaller members."¹⁴⁶

However, the decision about who is going to be the hosting country will not be taken by the EMA, thus it will be decided by a "common agreement" between the representatives of the MSs.¹⁴⁷ Therefore, since the moment UK will trigger the Article 50 of the Lisbon Treaty, a fierce two-year battle among the European capitals will be generated for the privilege in hosting the EMA institution.¹⁴⁸

C. Top Contenders for the EMA - A Battle of Looms¹⁴⁹

The Nordic countries, Sweden and Denmark, began preparing for the likelihood of BREXIT to happen in the early days of February 2016.¹⁵⁰ "Sweden's claims to eminence in the pharmaceutical and healthcare arena include the fact that it is home to the Karolinska Institute, which awards the Nobel Prize in medicine."¹⁵¹ Furthermore, Sweden is already the home of the European Centre for Disease Prevention and Control ("ECDC"), which could make it a logical choice for the new site of the EMA.¹⁵² "Despite its small size, Sweden is particularly well placed to become the next base for the EMA. On a political level, the country has relatively strong pro-EU credentials, and is regarded as politically and economically stable, and therefore a potential safe harbor for the medicines regulator."¹⁵³

Alternatively, Denmark announced its candidacy for the EMA with strong and insightful slogan: "The strong Danish tradition for safeguarding patient safety, an important research environment and a thriving and innovative pharmaceutical industry, Denmark has excellent preconditions for hosting the EMA".¹⁵⁴ "Denmark has one of the world's leading pharmaceutical industries, [because they already hosted] the WHO's Regional Office for Europe, [also] Copenhagen is a centrally located and [has a] dynamic bridge [in comparison] with to the rest of Europe."¹⁵⁵ In addition, "Denmark has a high-profile

supporter in its bid to become the new home of the EMA – the diabetes giant Novo Nordisk.¹⁵⁶ Furthermore, the Danish government delegated Lars Rebién Sørensen, former CEO of Novo Nordisk, as special envoy of the government.¹⁵⁷

Another top contender could be The Netherlands, which made their official bid by offering the EMA and its staff a new and impressive location.¹⁵⁸ The Government strongly points out that “the Dutch Medicines Evaluation Board (CBG) is a major contributor of expertise to the European network of pharmaceutical authorities coordinated by [the] EMA”.¹⁵⁹ Furthermore, Bert Koenders, Dutch foreign minister, said: “We are conveniently situated, with excellent transport links and we also have expertise in hosting international organizations.”¹⁶⁰

“Ireland emerges as a strong outside contender.”¹⁶¹ The Irish government, supported by the pharmaceutical division of its influential lobby, the Irish Business and Employers Confederation (“IBEC”), has joined the cluster of countries that expressed a strong interest in hosting the EMA.¹⁶² When manufacturing presence is taken into account, “the country is currently home to over seventy-five pharmaceutical companies, including nine of the top ten-pharma companies globally, and forty FDA-approved pharma and biopharma plants.”¹⁶³ Also as of 2014, “Ireland was the seventh largest exporter of medicines and pharma products in the world.”¹⁶⁴ According to Tommy Fanning, head of biopharmaceuticals for IDA Ireland “[I]n the last 10 years, there have been over \$10 billion in biologics manufacturing investments in Ireland highlighting Shire’s \$400 million investment in a 400-person biologics facility announced earlier this year.”¹⁶⁵ Moreover, Bristol-Myers Squibb, a global pharmaceutical company, has announced its plans to build a \$900 million facility in Ireland and to hire 500 people.¹⁶⁶ Definitely, the transition from London to Dublin would be much easier and without causing major disruption in its process given the background and connections the two capitals already share, and the fact that Dublin can be viewed as an “epitome of multilingual cultures.”¹⁶⁷

Italy also is vying to become the EMA’s new home and had emerged as a strong challenger because Italians constitute a high proportion of the agency’s permanent workforce, (12.36%),¹⁶⁸ and the EMA’s present CEO is Italian, Mr. Guido Raisi.¹⁶⁹ Italy ranks second after France (12.77%) and ahead of Spain (10.51%) with the highest proportion of full-time EMA staff.¹⁷⁰ Government officials in Milan are believed to have identified a site near the Human Technopole EXPO research and exhibition Centre on health and ageing as a possible future location for the EMA. The EUR 1.5 billion (USD 1.6 billion) multi-phase project is scheduled for completion by 2040.¹⁷¹

However, the strength of Italy’s effort is weakened “by the rise of populist political parties led by the Five Star Movement (Movimento 5 Stelle: M5S) and a significant weakening of the main centrist parties on both the center-right and center-left of Italian politics”¹⁷². Which can build an unstable climate for the Agency given the fact that “M5S are building for an in-out referendum on Italy’s membership of the EU.”¹⁷³

IV. A LAW-POLICY PROPOSAL FOR THE EU TO WIELD DAMOCLES' SWORD TO ENSURE PHARMACOVIGILANCE POST-BREXIT

The patients in the EU and their providers deserve nothing less than reliable pharmacovigilance over the medications the EMA has deemed safe and efficacious—medications they are taking in their daily lives.

While immediate and direct intervention regarding EMA's status is required and needed, as soon as possible, in order to ensure no disruption of ongoing regulatory oversight of prescription medications available to patients across Europe. Also, to give assurances of safety and efficacy for its particular pharmacovigilance function.¹⁷⁴ It is impracticable at this time while the UK's Government just exercised its right profiled in Article 50 of TEU and notified the office of European Council President, Donald Tusk about their withdrawal intentions, and the process can take up to two years.¹⁷⁵

Correspondingly, with Article 50, second paragraph, after the notification, the EU will negotiate an agreement with the withdrawing State in accordance with Article 218(3) of the Treaty on the Functioning of the EU ("TFEU").¹⁷⁶ These arrangements should also cover the departing MSs future relationship with the Union.¹⁷⁷ In addition, the Union and the MS wishing to withdraw have a time frame of two years to agree on these arrangements.¹⁷⁸ After that, membership ends automatically, unless the European Council and the MS concerned jointly decide to extend this period (Article 50(3) TEU).¹⁷⁹

Furthermore, before concluding the arrangements the consent of the European Parliament is required, states the second paragraph of Article 50 TEU.¹⁸⁰ In the end the final agreement will be taken by the European Council with a qualified majority in accordance with Article 238(3)(b) of the TFUE.¹⁸¹

The immediate effect of this agreement will be the suspension of all EU [laws] that have direct effect.¹⁸² Ergo, the Regulation (EC) No. 726/2004¹⁸³ that contains all the provisions regarding the legal foundations of the EMA, hence, all the legal basis of the EMA will cease to apply in the UK. However, their emergence and magnitude will very much depend on the withdrawal negotiations and the post-exit relationship between the withdrawing MS and the EU.¹⁸⁴ Therefore, unless the UK Parliament adopts a substantial law that can replace the current EU Regulation regarding the EMA, after the two-year agreement negotiation passes, there will be no legal foundation to keep the Agency in London given the fact that the withdrawing agreement will suspend all EU Regulations in the withdrawing State. In addition, if the Regulation (EC) No. 726/2004 will be suspended there will be no legal basis for the EMA to function in the UK. However, the secondary sources, such as the Directive 2012/26/EU, regarding the pharmacovigilance function,¹⁸⁵ will not be affected given the fact it did not have direct effect in the first place and the MSs had to regulate it through national laws which will still be applicable regardless of the agreement negotiated based on Article 50 of TEU.¹⁸⁶ Until the national authorities decide to amend or repeal them.¹⁸⁷

Having all that in mind the EMA board already approved a slightly increased budget for 2017 in order to prepare for the UK's departure from the EU.¹⁸⁸ As part of its

preparedness, “the Agency will continue carrying out impact assessments to identify the main risks and propose possible mitigating measures to maintain the Agency’s ability to protect public health.”¹⁸⁹

Therefore, as a first proposal, this paper recommends that the EU prioritize and implement a transitional regulatory reform on the acquired rights of the EMA.¹⁹⁰ To protect the pharmacovigilance mission and function of the EMA during the Agency’s state of post-BREXIT transition. “The arrangements for the withdrawal could aim at attenuating its consequences over the Agency, including transitional application of some EU legislation in the withdrawing state,”¹⁹¹ to protect its very mission, ongoing oversight of the EU market during the transition. Also, immediately there should be a EU agreement reached to keep this function of the EMA intact and centralized in London for a period of time, as a temporary measure, so that would give the Agency time to shift all the operations to the new host country.

A second visualize scenario could be the so-called “Norway model (sometimes called associate membership): the UK would remain inside the EU but with a more separate status than now, rather than trying to re-connect with the EU after leaving it.”¹⁹² Moreover, in this way the UK Government could lobby during the negotiations to keep the EMA in London as a permanent measure.¹⁹³

The *Blitzkrieg* Proposal – A New Host Country

A third proposal, implicates moving the EMA from London to a new host country, this paper suggests that the EU institutions should prioritize and act in a *blitzkrieg* manor and shift the operations of the EMA, even from the beginning of withdrawal negotiations, to the new host country, rather than wait for the whole two years’ timeframe of the negotiations to reach an agreement. The two-year period could have a highly negative impact on its pharmacovigilance function that can cause major disruption and can pose an enormous public health threat on both the health care providers and their patients in the European market.¹⁹⁴

Even though there are other countries that have a solid background in their health care system, countries like Germany, Sweden, The Netherlands, even France or Italy, this paper proposes the new host country to be Denmark for the following reasons.

The Danish health care system offers, by far, the strongest and the most persuasive argument to foster the EMA post BREXIT. Copenhagen offers an excellent research environment, “where expertise and easy access to both researchers and professional research collaboration will be an excellent setting for the activities of the EMA.”¹⁹⁵ In addition, “[i]n terms of investment in R&D, Denmark is the only country among the EU members that invest the most public funds in R&D per capita.”¹⁹⁶ “Medical and health sciences are by far the most prioritized research area in Denmark, with more than thirty-three per cent of all public investments going into this scientific field.”¹⁹⁷ Furthermore, “[t]here is also a long-standing tradition and solid foundation for pharmaceutical research in Denmark, moreover, they already facilitated the establishment of a cluster of biotech companies in Medicon Valley.”¹⁹⁸

Second argument could be made by its “innovative and vibrant life science cluster albeit the not only the R&D but also the manufacturing of pharmaceutical products represent Denmark’s commercial strength.”¹⁹⁹ Among the EU MSs, “Denmark ranks sixth with regard to foreign investments per capita in pharmaceuticals and biotechnology.”²⁰⁰ Furthermore, “Denmark ranks number one among the EU MSs in terms of private investments in pharmaceutical research per capita.”²⁰¹ As the EMA does, Denmark also adopted a strong standard to protect public health and to prioritize patient safety, “[by introducing] a compulsory system for reporting adverse events in healthcare in order to improve patient safety through the monitoring, analysis and knowledge sharing of adverse events.”²⁰²

Aside from its highly known infrastructure, Denmark provides a multicultural environment where the workforce is “skilled and efficient and it can thus constitute a qualified, local supplement to the EMA’s international staff when required.”²⁰³ In addition, “health science is the field with the highest number of PhDs awarded in Denmark, which underlines Denmark’s specialization in this area.”²⁰⁴ All these qualities will be of great importance in order to secure a successful and smooth relocation of the EMA.²⁰⁵

V. Conclusion

The EU, its patients, providers, and health care systems, depend on consistent, ongoing EMA pharmacovigilance function.²⁰⁶ Now more than ever, in an age of infusion of technology and complexity any shattering of focus in its operations and fundamental functions can pose a major disruption to its very core and can cause an enormous threat on the EU public health.²⁰⁷ It is needless to say that the biopharmaceutical sectors and enormous related professional infrastructure that towers over the EMA, anchored in London from its beginning, now stands on shifting soil. Fifteen per cent of all applications via the centralised procedure are currently handled by the UK Medicines and Healthcare Product Regulatory Agency (“MHRA”), the UK notified body.²⁰⁸ These would have to be redistributed amongst the remaining notified bodies.²⁰⁹

Furthermore, half of the EMA’s staff left the Agency since the BREXIT decision the so-called “brain drain”. Alongside the economic and social implications, the disruption over the pharmacovigilance reliability, decision-making, the professional and scientific expertise to make those decisions, are the most critical ones.²¹⁰ If Brexit results in less co-operation and sharing of expertise and information, the resulting pharmacovigilance would be less efficient and more costly.²¹¹

This paper proposes that the EU prioritize and implement regulatory reform measures to protect this particular mission and function of the EMA during the Agency’s state of post-BREXIT transition. The paper proposes that pharmacovigilance is distinguishable and should be prioritized given the ongoing reliance of health care providers and their patients on these products under the regulatory assurances of safety, efficacy, and ongoing oversight that have made them available for treatment us.

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¹ Paper submitted in partial fulfillment of the requirements for the degree of LL.M., Paul M. Hebert Law Center, Louisiana State University.

Acknowledgements:

My sincere gratitude to Professor Dr. Mircea Dan-Bob, without whom I would not have the privilege to study in this LL.M. program and write the said thesis. In addition, I would like to express my appreciation and gratefulness to recently passed away Professor A. N. Yiannopoulos and its fellowship foundation for the financial support and the honor to be part of the Yiannopoulos endowed scholarship.

J'aimerais également dire toute ma sincère gratitude à, mon Professor, Dr. Olivier Moréteau pour tout le support et le guidage au cours du programme et pour toutes les choses que j'ai appris, merci beaucoup.

I want to express my sincere gratitude to my supervisor, Professor Michael J. Malinowski, for his endless support, encouragement and guidance throughout this thesis without who this project would not be possible, thank you.

Finally, yet importantly, I am thankful to all my relatives and friends for their unwavering moral and emotional support.

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- ² See generally EMA, official site, available at <http://www.ema.europa.eu/ema/> (last visited 18th of February 2017).
- ³ Although each has an independent regulatory gatekeeper, there is much regulatory coordination such as data acceptance and good manufacturing practices through the International Conference of Harmonization (“ICH”) Visit ICH, official site, available at <http://www.ich.org/home.html> (last visited 18th of February 2017).
- ⁴ See generally the mission of the EMA, official site, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42 (last visited 2nd of April 2017).
- ⁵ *Id.*
- ⁶ For a more detailed and substantial analysis over the genomics revolution and the Human Genome Project. See Michael J. Malinowski, Handbook on Biotechnology Law, Business and Policy, WEST ACADEMIC PUBLISHING 13, (2016). Even though the genomics revolution began globally with the new informatics industry just lunched it’s important to give full credit to the USA for being the core of it, by investing so many resources and realizing such an illustrious achievement for the human race, mapping the human genome which was made possible by the fact we are 99.9 percent the same genetically. *Id.* at *Science Primer*. Also see generally, Jessica Alföldi, Kerstin Lindblad-Toh, Comparative genomics as a tool to understand evolution and disease, available at <http://genome.cshlp.org/content/23/7/1063.full#aff-2> (last visited 28th of February 2017).⁶ See National Human Genome Research Institute (NHGRI), an overview of the Human Genome Project (2012), available at <http://www.genome.gov/12011239> (with links to related sources). The future for genomic medicines is bright, and its circle of shining light is intensifying and expanding with advancement of the underlying science. Biologics are introducing the means to provide care for complex, life-threatening diseases for which no sufficient treatment exists, including cancer and auto-immune disorders such as multiple sclerosis and Crohn’s disease. See generally Lacie Glover, Why Are Biologic Drugs So Costly? A Look at How Biologics Are Made, How Much They Cost and Why, U.S. NEWS (Feb. 6, 2015), available at <http://health.usnews.com/health-news/health-wellness/articles/2015/02/06/why-are-biologic-drugs-so-costly> (last visited 27th of March 2017).
- ⁷ See generally information about Vistide, EMA official site, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000121/human_med_001145.jsp&mid=WC0b01ac058001d124 (last visited 2nd of April 2017).
- ⁸ Its purpose was to treat the effects of the disease, which can cause loss of vision. Vistide is used in patients with acquired immunodeficiency syndrome (“AIDS”) who do not have kidney disease. See generally EMA, official site, summary for the public, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000121/WC500052073.pdf (last visited 18th of February 2017).
- ⁹ The centralized procedure allows the marketing of a medicine based on a single EU-wide assessment and marketing authorization, which is valid throughout the EU. For more details about the centralized procedure see generally Chapter 2, Subsection A, *infra*.
- ¹⁰ European Commission Decision, available at <http://ec.europa.eu/health/documents/community-register/html/h037.htm> (last visited 18th of February 2017).
- ¹¹ For more details, see generally EMA, official site, List of withdrawn medicinal products, 30 January 2015, available at <http://www.ema.europa.eu/ema/> (last visited 18th of February 2017). See also Official Statement by the EMA, available at http://www.ema.europa.eu/docs/en_GB/document_library/

- Supply_shortage/2013/11/WC500153782.pdf (last visited 18th of February 2017). In addition, the difference between the EU market/EMA v. the U.S. and FDA is that typically in the U.S., with no “second gate” to uptake through individual health services, withdrawals are much more frequently mandated, either directly by the FDA or through FDA demands of issuance of warning letters. See generally FDA, official site, available at <https://www.fda.gov/>.
- ¹² The Decision is available at <http://ec.europa.eu/health/documents/community-register/html/h037.htm> (last visited 18th of February 2017).
- ¹³ See generally EMA, official site, Summary for the public, available at http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2015/10/WC500194593.pdf (last visited 6th of March 2017).
- ¹⁴ See Symposium, *Proceedings of “The Genomics Revolution? Science, Law, and Policy*, 66 LA. L. REV. 1, 2 (2005).
- ¹⁵ The medical product is made of stem cells from the umbilical cord. *Id.* For comprehensive understanding of the science and law and policy behind the human embryonic stem cells (“hESCs”) see also Malinowski, *supra* note 3, at Science Primer xx, 16-17.
- ¹⁶ European Commission Decision, *supra* note 9.
- ¹⁷ See general information about the Orphan designation, EMA official site, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/10/human_orphan_001639.jsp&mid=WC0b01ac058001d12b (last visited 2nd of April 2017)
- ¹⁸ For more details about the disease see National Cancer Institute, official website, available at <https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq> (last visited 13th of March 2017). See also American Cancer Society, official site, available at <https://www.cancer.org/cancer/acute-myeloid-leukemia/about/what-is-aml.html> (last visited 13th of March 2017).
- ¹⁹ *Id.*
- ²⁰ European Commission, official site, available at <http://ec.europa.eu/health/documents/community-register/html/o1546.htm> (last visited 19th of February 2017).
- ²¹ *Id.*
- ²² See *supra* the previous two examples given.
- ²³ See generally The European regulatory system for medicines leaflet published by EMA, official site, available at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf (last visited 13th of March 2017)
- ²⁴ See generally FDA Fundamentals, official site, available at <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm> (last visited 2nd of April 2017).
- ²⁵ Professor Michael J. Malinowski, Biotechnology course, Paul M. Herbert Law Center, Louisiana State University, 2017.
- ²⁶ *Id.*
- ²⁷ Pain medication for instances at least somewhat already treatable. See generally information about Vioxx, available at <https://www.drugs.com/vioxx.html> (last visited 16th of March 2017).
- ²⁸ See generally FDA, official site, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21042lbl.pdf (last visited 16th of March 2017).
- ²⁹ FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product, available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108361.htm> (last visited 16th of March 2017).

- ³⁰ See Alternatives to Vioxx if Heart Disease Present — TheFamily HealthGuide, available at <http://www.health.harvard.edu/heart-health/alternatives-to-vioxx-if-heart-disease-present--thefamily-healthguide> (last visited 16th of March 2017).
- ³¹ Why Vioxx played out differently in each market? See Michael J. Malinowski & Grant G. Gautreaux, "Drug Development--Stuck in a State of Puberty? Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability, 56 ST. LOUIS U. L. J. 363" (2012). Available at http://digitalcommons.law.lsu.edu/faculty_scholarship/50 (last visited 2nd of April 2017).
- ³² See generally European Medicines Agency statement following withdrawal of Vioxx (rofecoxib), available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000352.jsp&mid=WC0b01ac058004d5c1 (last visited 16th of March 2017).
- ³³ See FDA, official site, available at <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm> (last visited 16th of March 2017).
- ³⁴ See generally Vioxx Recall Information, available at <https://www.drugwatch.com/vioxx/recall/> (last visited 16th of March 2017).
- ³⁵ See *infra* The EMA's Law Origins and Fundamentals regarding the definition of pharmacovigilance. See also *infra* note 55.
- ³⁶ See generally EMA's Annual Report 2015, official website, available at http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf (last visited 13th of March 2017).
- ³⁷ Its Pharmacovigilance system, the EudraVigilance system, The European Risk Management Strategy ("ERMS"), Good Pharmacovigilance Practice ("GVP"), etc.
- ³⁸ Malinowski, *supra* note 5, at Preface.
- ³⁹ Doctor Francis Collins, director of National Institute of Health ("NIH"), respected and brilliant scientist once said that "Iron sharpens iron", and the EMA can be considered an iron that needs constant sharpness, available at <https://www.brainyquote.com/quotes/quotes/f/franciscol555127.html> (last visited 11th of April 2017).
- ⁴⁰ Meaning the safety, effectiveness, and overall ongoing oversight of prescription medications approved for market use. See *infra* The EMA's Law Origins and Fundamentals regarding the definition of pharmacovigilance.
- ⁴¹ Regulations, as a secondary legislation source under the EU – see generally, Articles 289, 290 and 291 from the Treaty on the Functioning of the EU [hereinafter TFEU] which establish a hierarchy of secondary legislation between legislative acts, delegated acts and implementing acts – have binding force throughout every Member State as soon as they enter into force and do not need to be transposed into national law. Whereas, the Directives, which lay down certain results that must be achieved, but each Member State is free to decide how to transpose directives in their national laws. For more details about the sources and the scope of the EU law, see also, European Parliament, official site, available at http://www.europarl.europa.eu/ftu/pdf/en/FTU_1.2.1.pdf (last visited 25th of February 2017).
- ⁴² Regulation (EC) No. 726/2004 of the European Parliament and of the Council, of 31 march 2004, O.J. (L 136). Was replaced because "in the light of the Commission's report on the experience gained, it has proved necessary to improve the operation of the authorization procedures for the placing of medicinal products on the market in the Community and to amend certain administrative aspects of [the Agency]", paragraph two of the said Regulation. European Commission, official site, available at http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (last visited 25th of February 2017).

- ⁴³ Because the No. 726/2004 Regulation is the current law, it will be cited from now on whilst leaving the old aside. For more details about the No. 2309/93 Regulation, see generally European Commission, official site, available at http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_1993_2309/reg_1993_2309_en.pdf (last visited 25th of February 2017).
- ⁴⁴ See *supra*, EMA, official site, see also, Herwig C. H. Hofmann, *Agency Design in the European Union*, 28 Windsor Y.B. Access Just. 309, 324 (2010); see also, Aurelie Mahalatchimy; Emmanuelle Rial-Sebbag; Nathalie De Grove-Valdeyron; Virginie Tournay; Anne Cambon-Thomsen; Anne-Marie Duguet; Florence Taboulet, *The European Medicines Agency: A Public Health European Agency*, 31 Med. & L. 25, 42 (2012).
- ⁴⁵ Malinowski, *supra* note 5, 127.
- ⁴⁶ See generally FDA, official website, available at <https://www.fda.gov/> (last visited 14th of March 2017).
- ⁴⁷ *Id.*
- ⁴⁸ See *supra* note twenty-three addressing FDA's ongoing oversight and recalls. Also, see *supra* *Introduction Chapter* regarding EMA's ongoing oversight and recalls function.
- ⁴⁹ See *supra* note 20, at Article 55.
- ⁵⁰ *Id.* at Article 57, paragraph 1, (a)-(s).
- ⁵¹ See The European regulatory system for medicines leaflet published by EMA, official site, available at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf (last visited 26th of February 2017).
- ⁵² The centralized procedure allows the marketing of a medicine based on a single EU-wide assessment and marketing authorization, which is valid throughout the EU. Pharmaceutical companies submit a single authorization application to EMA. The Agency's Committee for Medicinal Products for Human Use ("CHMP"), then carries out a scientific assessment of the application and gives a recommendation to the European Commission on whether or not to grant a marketing authorization. Once granted by the European Commission, the centralized marketing authorization is valid in all EU MSs. The use of the centrally authorized procedure is compulsory for most innovative medicines, including medicines for rare diseases. *Id.* at page 2; See also, the centralized procedure is "compulsory for high technology medicinal products, particularly those resulting from biotechnical processes, [t]his is particularly important in the context of the emergence of new therapies, such as gene therapy and associated cell therapies, and xenogenic somatic therapy, to ensuring the effective operation of the internal market in the pharmaceutical sector." Para. 7 from No. 726/2004 Regulation.
- ⁵³ The decentralized procedure is based on companies that can apply for the simultaneous authorization of a medicine in more than one EU Member State if it has not yet been authorized in any EU country and does not fall within the scope of the centralized procedure. See The European regulatory system for medicines leaflet published by the EMA, *supra*, at page 2.
- ⁵⁴ The mutual-recognition procedure can be used when companies that have a medicine authorized in one EU MSs can apply for this authorization to be recognized in other EU countries. This process allows MSs to rely on each other's scientific assessments. *Id.* See also, Mutual recognition in decentralized procedures between MSs, Chapter 4, Article 28, DIRECTIVE 2001/83/EC of The European Parliament and of The Council, of 6 November 2001, on the Community code relating to medicinal products for human use. O.J. (L 311). Available at http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf (last visited 26th of February 2017).
- ⁵⁵ The Agency published a 20th Anniversary Book, see generally EMA, official site, available at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2015/03/WC500184383.pdf (last visited February 26th 2017).

- ⁵⁶ Also called European Public Assessments Reports (EPAR) based on Article 13 (3) of No. 726/2004 Regulation, which requires the EMA to publish assessments reports for each medical product granted or refused a marketing authorization via the centralized procedure. *See generally* EMA, European public assessment reports: background and context, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&mid=WC0b01ac058067fa25 (last visited 28th of February 2017).
- ⁵⁷ The European Commission has the right of initiative by proposing or amending legislation in the pharmaceutical sector, it can adopt implementing measures as well as oversee the correct application of EU law on pharmaceuticals and it ensures appropriate collaboration with relevant international partners and promotes the EU regulatory system globally. *See* The European regulatory system for medicines leaflet published by EMA, *supra*, at 3.
- ⁵⁸ *Id.*
- ⁵⁹ Malinowski, *supra* note 5, at Preface. A detailed drug development continuum can be applied by analogy in the EMA's framework of medical products as well.
- ⁶⁰ Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions and other medicine-related problems. *See* EMA leaflet on Pharmacovigilance, official site, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2011/03/WC500104236.pdf (last visited 27th of February 2017).
- ⁶¹ *See* EMA, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&mid=WC0b01ac05801ae8fb# (last visited 27th of February 2017).
- ⁶² *See* EMA Pharmacovigilance legislation, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058058f32d (last visited 27th of February 2017).
- ⁶³ *Available at* <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF> (last visited 27th of February 2017).
- ⁶⁴ *Available at* <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF> (last visited 27th of February 2017).
- ⁶⁵ *See* Medscape Newspaper Article, *available at* <http://www.medscape.com/viewarticle/758430> (last visited 27th of February 2017); *see also* The Lancet, Vol 377 March 12, 2011, *available at* [http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(11\)60334-6.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(11)60334-6.pdf) (last visited 27th of February 2017).
- ⁶⁶ Benfluorex was used as an add-on treatment in patients with diabetes who are overweight. In a combination with an appropriate diet. Benfluorex works by making the cells more sensitive to insulin, which means that the body makes better use of the insulin it produces and the blood glucose is reduced. Following several reports of cardiac valvulopathy (thickening of the heart valves) and pulmonary arterial hypertension (high blood pressure in the artery that leads from the heart to the lungs) both French and Portuguese authorities recalled the medical product. *See* EMA, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Benfluorex/human_referral_000220.jsp&mid=WC0b01ac05805c516f (last visited 27th of February 2017).
- ⁶⁷ *Id.*
- ⁶⁸ *See supra* note 22.
- ⁶⁹ *See* PRAC strategy on measuring the impact of Pharmacovigilance activities, EMA official website, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf (last visited 15th of March 2017).

- ⁷⁰ A centralized European database of suspected adverse reactions to medicines that are authorized or being studied in clinical trials in the European Economic Area (“EEA”). For more information, see EMA EudraVigilance, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5 (last visited 2nd of April 2017).
- ⁷¹ See *supra* note 68.
- ⁷² *Id.*
- ⁷³ See *generally* EMA Good pharmacovigilance practices, official website, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c (last visited 15th of March 2017).
- ⁷⁴ *Id.*
- ⁷⁵ For a more detailed and substantial analysis over the genomics revolution and the Human Genome Project, see *id* at 13. Even though the genomics revolution began globally with the new informatics industry just lunched it is important to give full credit to the USA for being the core of it, by investing so many resources and realizing such an illustrious achievement for the human race, mapping the human genome which was made possible by the fact we are 99.9 percent the same genetically. *Id* at *Science Primer*; see also, Jessica Alföldi, Kerstin Lindblad-Toh, Comparative genomics as a tool to understand evolution and disease, *available at* <http://genome.cshlp.org/content/23/7/1063.full#aff-2> (last visited 28th of February 2017).
- ⁷⁶ *Id* at 135.
- ⁷⁷ See 10-year report highlights published by the EMA, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/01/WC500219993.pdf (last visited 4th of March 2017).
- ⁷⁸ Product groups on which EMA published assessment reports (“EPAR”) based on Article 13 (3) of No. 726/2004 Regulation, which requires the EMA to publish assessments reports for each medical product, granted or refused a marketing authorization via the centralized procedure. See *generally*, EMA, European Public Assessment Reports: Background and Context, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&mid=WC0b01ac058067fa25 (last visited 28th of February 2017).
- ⁷⁹ Similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. See *generally* Biosimilar medicines EMA, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac0580281bf0 (last visited 2nd of April 2017).
- ⁸⁰ See EMA’s Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3), at 9, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf (last visited 15th of March 2017).
- ⁸¹ Because biologics are introducing the means to provide care for complex, life-threatening, and otherwise seriously life-debilitating diseases for which no sufficient treatment exists, including cancers and autoimmune disorders such as multiple sclerosis and Crohn’s disease. Malinowski, *supra* note 3 at xxi
- ⁸² Terry G. Mahn & Dr. Gauri M. Dhavan, *Biosimilars vs. Generics – Major Differences in the Regulatory Model*, *Pharma*. COMPLIANCE MONITOR (identifying similarities and differences between generics and these new classes of drugs), *available at* <http://www.pharmacompliancemonitor.com/biosimilars-vs-generics-major-differences-in-the-regulatory-model/> (last visited 2nd of April 2017).

- ⁸³ See EMA, official site, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&keyword=humira&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=generics&genericKeywordSearch=Submit (last visited 28th of February 2017).
- ⁸⁴ *Id* at Biosimilar (browse by type).
- ⁸⁵ For drug development pipeline visit the internet sites of Pharmaceutical Researchers and Manufacturers of America (“PhARMA”), the world leading pharmaceutical trade organization, *available at* <http://www.phrma.org/> (last visited 4th of March 2017). The Biotechnology Industry Organization (BIO), the worlds’ leading biotechnology industry trade organization, *available at* <https://www.bio.org/> (last visited 4th of March 2017). Malinowski, *supra* note 3, at 96.
- ⁸⁶ See *supra* note 43, at 63.
- ⁸⁷ *Id.* at 86.
- ⁸⁸ *Id.*
- ⁸⁹ See EU and the UK after the referendum on 23 June 2016, Timeframe, European Commission, official site, *available at* http://www.consilium.europa.eu/en/policies/eu-uk-after-referendum/?utm_source=facebook.com&utm_medium=social&utm_campaign=29032017_brexit&utm_content=animation (last visited 28th of March 2017).
- ⁹⁰ In a referendum on 23 February 1982, Greenland decided – by 53% to 47% – to leave the then European Communities (EC). However, the 1985 'exit' of Greenland from the EC is legally speaking not a 'withdrawal' as Greenland was not a Member State of the EU but was, and remains, part of an EU Member State, Denmark. So Greenland cannot be held as a withdrawal precedent. See *generally* European Parliament Brief on Article 50 TEU, official site, *available at* [http://www.europarl.europa.eu/RegData/etudes/BRIE/2016/577971/EPRS_BRI\(2016\)577971_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/BRIE/2016/577971/EPRS_BRI(2016)577971_EN.pdf) (Last visited 3th of March 2017).
- ⁹¹ See UK Government, official site, *available at* <https://www.gov.uk/government/topical-events/eu-referendum> (Last visited 3th of March 2017).
- ⁹² The decision to pool the coal and steel industries of six European countries, [after the disastrous effects of the World War II] brought into force by the Treaty of Paris, the Treaty establishing the European Coal and Steel Community (ECSC), in 1951, symbolized the birth of a common purpose and marked the first step towards European integration. The Treaties of Rome of 1957, The Treaties establishing the European Economic Community (EEC) and the European Atomic Energy Community (EAEC, otherwise known as “Euratom”), strengthened the foundations of this integration and the notion of a common future for the six European countries involved and conferred quasi-constitutional status on them. The six founding countries were Belgium, France, Germany, Italy, Luxembourg and the Netherlands. See European Parliament, official site, *available at* http://www.europarl.europa.eu/ftu/pdf/en/FTU_1.1.1.pdf (Last visited 3th of March 2017).
- ⁹³ The UK joined on 1 January 1973, together with Denmark and Ireland. *Id* at http://www.europarl.europa.eu/ftu/pdf/en/FTU_1.1.2.pdf (Last visited 3th of March 2017).
- ⁹⁴ See *supra* note 88. See also John Fairhurst, *Law of the European Union*, 47, 8th Edition, Pearson Education Limited, (2010).
- ⁹⁵ See *supra* note 88 at 2.
- ⁹⁶ See *generally* David Edward & Robert Lane, *Edward and Lane on European Union Law*, 80-83, Edward Elgar Publishing Limited, (2013).

⁹⁷ See *supra* note 88 at 3.

⁹⁸ *Id.*

⁹⁹ *Id.* at 4.

¹⁰⁰ The myriad other issues, like review and approvals, and implications are beyond the scope of the paper.

¹⁰¹ See *supra* Background Chapter, The EMA's Law Origins and Fundamentals; see also *infra* note 115, about the National Human Genome Research Institute, media coverage of biologics/genomics in new drug development and the amazing accomplishments in oncology; see also Brexit's Impact on Healthcare and Life Sciences, available at <http://www.fticonsulting.com/~media/Files/emea--files/insights/articles/brexit-impact-healthcare.pdf> (last visited 29th of March 2017).

¹⁰² The overall implications are immense and beyond the scope of this paper.

¹⁰³ See *infra*. The EMA has also been aligning its policies with the U.S. FDA to make it easier for companies to submit applications to both the European and U.S. markets. As such, many experts predict that Brexit could hamper drug innovation in the UK. The impact of Brexit on the health care and life sciences industries, available at <https://www.grantthornton.com/~media/content-page-files/advisory/pdfs/2016/brexit/Brexit-industry-update-HCLS-160711.ashx> (last visited 29th of March 2017).

¹⁰⁴ CBER's mission is to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms), are not easily identified or characterized, and many are manufactured using biotechnology. See generally FDA, official site, About CBER, available at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123340.htm> (last visited 30th of March 2017).

¹⁰⁵ See *supra* Background Chapter, The EMA's Law Origins and Fundamentals.

¹⁰⁶ *Id.*

¹⁰⁷ *Id.*

¹⁰⁸ See generally *infra*, EMA's infrastructure and its potential disruption; see also *infra*, The overall impeding effect of BREXIT on the EMA as regulatory body and its potential new home.

¹⁰⁹ See *infra* EMA's Infrastructure and Its Potential Disruption; see also note 121, London-based regulator for EU drugs fears staff exodus.

¹¹⁰ *Id.*

¹¹¹ See generally Why losing the European Medicines Agency is bad news for patients, jobs – and the NHS, available at <https://www.theguardian.com/science/political-science/2016/oct/14/why-losing-the-european-medicines-agency-is-bad-news-for-patients-jobs-and-the-nhs> (last visited 17th of March 2017).

¹¹² See *supra* note 54, at 35.

¹¹³ *Id.* at 56.

¹¹⁴ See 1995-2015 Working together for safe and effective medicines leaflet, available at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2015/05/WC500186917.pdf (last visited 17th of March 2017).

¹¹⁵ For more details, see *supra* Background Chapter.

¹¹⁶ *Id.*

¹¹⁷ See *supra* note 54, at 52.

¹¹⁸ See EMA's 2015 Annual Report, at 90, available at http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf (last visited 17th of March 2017).

¹¹⁹ Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ L 189 p. 112 27.06.2014.

¹²⁰ See *supra* note 117, at 91.

¹²¹ *Id.* at 81.

¹²² London-based regulator for EU drugs fears staff exodus, *available at* <https://www.ft.com/content/2ca416ba-c8f8-11e6-8f29-9445cac8966f> (last visited 17th of March 2017).

¹²³ *Id.*

¹²⁴ *Id.*

¹²⁵ *Id.*

¹²⁶ See *generally* Brexit ‘an opportunity,’ but EMA likely to leave London, says AstraZeneca, *available at* <http://www.fiercebiotech.com/biotech/brexit-opportunity-but-ema-likely-to-leave-london-says-astrazeneca> (last visited 17th of March 2017).

¹²⁷ *Id.*

¹²⁸ See At least seven countries are jockeying to host EU's medicine watchdog after United Kingdom leaves, *available at* <http://www.sciencemag.org/news/2017/01/least-seven-countries-are-jockeying-host-eus-medicine-watchdog-after-britain-leaves> (last visited 18th of March 2017).

¹²⁹ See *generally*, Japan to U.K.: Keep EMA post-Brexit or our drug makers may move R&D to mainland Europe, *available at* <http://www.fiercebiotech.com/biotech/japan-to-u-k-keep-ema-post-brexit-or-our-drugmakers-may-move-r-d-to-mainland-europe> (last visited 17th of March 2017).

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² See EMA official statement, *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002566.jsp&mid=WCOb01ac058004d5c1 (last visited 18th of March 2017).

¹³³ See National Human Genome Research Institute (NHGRI), An overview of the Human Genome Project (2012), *available at* <http://www.genome.gov/12011239> (with links to related sources). The future for genomic medicines is bright, and its circle of shining light is intensifying and expanding with advancement of the underlying science. Biologics are introducing the means to provide care for complex, life-threatening diseases for which no sufficient treatment exists, including cancer and autoimmune disorders such as multiple sclerosis and Crohn's disease; see *generally* Lacie Glover, Why Are Biologic Drugs So Costly? A Look at How Biologics Are Made, How Much They Cost and Why, U.S. NEWS (Feb. 6, 2015), *available at* <http://health.usnews.com/health-news/health-wellness/articles/2015/02/06/why-are-biologic-drugs-so-costly> (last visited 27th of March 2017); see also *supra*, the Background Chapter, The EMA's Pharmacovigilance Assessments. See also FDA, Information for Consumers (Biosimilars), *available at* <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm> (last updated: 27th of August 2015).

¹³⁴ The cost for development of a new medicine is about €1 billion and it takes on average 12-13 years for a new active substance to reach the EU market; see The work of the European Medicines Agency, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2016/10/WC500214054.pdf (last visited 17th of March 2017). The immediate significance of the reliability of approvals already made is not the equivalent of making new ones—the former already are being used with expectations of safety, efficacy. The longer-term effects may very well be more significant on the review and approval side, but this paper is focusing on pharmacovigilance. The above paragraph has the purpose to show that other fundamental functions of the EMA will be affected by the potential disruption.

¹³⁵ See *supra* note 121, London-based regulator for EU drugs fears staff exodus.

- ¹³⁶ The myriad of other issues and implications are beyond the scope of the paper.
- ¹³⁷ See E.U. Agency in Limbo as Hidden Costs of ‘Brexit’ Continue to Mount, *available at* https://www.nytimes.com/2016/12/25/world/europe/eu-medicines-agency-britain-brexit.html?_r=1#story-continues-1 (last visited 18th of March 2017).
- ¹³⁸ *Id.*
- ¹³⁹ See *supra* note 133.
- ¹⁴⁰ See Pharmaceutical Innovation in Europe, figure 1, *available at* <http://info.evaluategroup.com/rs/607-YGS-364/images/2016-EDF-Pharma-Innovation.pdf> (last visited 18th of March 2017).
- ¹⁴¹ See *supra* note 133.
- ¹⁴² See EU members line up to host EMA headquarters, regulator seeks to calm pharma sector by reporting business as usual, *available at* <https://www.ihs.com/country-industry-forecasting.html?ID=10659116441> (last visited 18th of March 2017).
- ¹⁴³ See Bidding war over lucrative Brexit spoil, *available at* <http://www.politico.eu/article/bidding-war-for-europes-medicines-regulator-kicks-into-high-gear-ema-brexit-drug-regulator-uk-eu/> (last visited 18th of March 2017).
- ¹⁴⁴ *Id.*
- ¹⁴⁵ *Id.*
- ¹⁴⁶ See *supra* note 141, EU members line up to host EMA headquarters, regulator seeks to calm pharma sector by reporting business as usual.
- ¹⁴⁷ See *supra* note 91; see *generally supra*, Section C, Background Chapter, The Legal Consequences of the BREXIT Decision – Short Overview of Article 50 of TEU.
- ¹⁴⁸ *Id.*
- ¹⁴⁹ See Battle Looms Over Relocation of EU Medicines Agency, *available at* <http://www.relocatemagazine.com/news/battle-looms-over-relocation-of-eu-medicines-agency-david-sapsted> (last visited 19th of March 2017).
- ¹⁵⁰ See Swedish Industry Wants European Medicines Agency if UK quits EU, *available at* <http://www.reuters.com/article/us-britain-eu-medicines-idUSKCN0VZ25P> (last visited 19th of March 2017)
- ¹⁵¹ *Id.*
- ¹⁵² See Sweden Joins Campaign for Post-Brexit Host of EMA, *available at* <http://xtalks.com/Sweden-for-Post-Brexit-Host-of-EMA-590.ashx> (last visited 19th of March 2017).
- ¹⁵³ See *supra* note 141, EU members line up to host EMA headquarters, regulator seeks to calm pharma sector by reporting business as usual.
- ¹⁵⁴ See The Danish Government’s press release about Denmark’s candidacy for hosting the EMA, official site, *available at* <http://um.dk/en/news/NewsDisplayPage/?newsID=1B20AB10-35B9-4B7C-A2AD-17048E2CF4D2> (last visited 19th of March 2017).
- ¹⁵⁵ *Id.*
- ¹⁵⁶ See Denmark’s EMA Bid Backed by Novo Nordisk, *available at* <https://www.thepharmaletter.com/article/denmark-s-ema-bid-backed-by-novo-nordisk> (last visited 19th of March 2017).
- ¹⁵⁷ See *generally*, Former Novo CEO is Denmark’s joker in the fight for EMA, *available at* http://medwatch.dk/Top_picks_in_english/article9351299.ece (last visited 9th of April 2017).
- ¹⁵⁸ See Government wants European Medicines Agency to relocate to the Netherlands, official site, *available at* <https://www.government.nl/latest/news/2017/01/16/government-wants-european-medicines-agency-to-relocate-to-the-netherlands> (last visited 19th of March 2017).
- ¹⁵⁹ *Id.*

- ¹⁶⁰ See European Regulatory Roundup: The Netherlands Bids to Host EMA (20 January 2017), available at <http://www.raps.org/Regulatory-Focus/News/2017/01/20/26650/European-Regulatory-Roundup-The-Netherlands-Bids-to-Host-EMA-20-January-2017/> (last visited 19th of March 2017).
- ¹⁶¹ See *supra* note 141, EU members line up to host EMA headquarters, regulator seeks to calm pharma sector by reporting business as usual
- ¹⁶² *Id.*
- ¹⁶³ See The Case for Moving The EMA to Ireland, available at <https://www.biosimilardevelopment.com/doc/the-case-for-moving-the-ema-to-ireland-0001> (last visited 19th of March 2017).
- ¹⁶⁴ *Id.*
- ¹⁶⁵ *Id.*
- ¹⁶⁶ *Id.*
- ¹⁶⁷ *Id.*
- ¹⁶⁸ See *supra* note 115, at 92.
- ¹⁶⁹ See *supra* note 141, EU members line up to host EMA headquarters, regulator seeks to calm pharma sector by reporting business as usual.
- ¹⁷⁰ *Id.*
- ¹⁷¹ *Id.*
- ¹⁷² *Id.*
- ¹⁷³ *Id.*
- ¹⁷⁴ See generally Michael J. Malinowski & Grant G. Gautreaux, *All that is Gold Does Not Glitter in Human Clinical Research: A Law – Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development*, 45 Cornell Int’l L.J. 185 (2012), available at http://digitalcommons.law.lsu.edu/faculty_scholarship/54 (last visited 24th of March 2017).
- ¹⁷⁵ The UK’s Permanent Representative to the EU, Sir Tim Barrow, has informed on 20th of March 2017, the office of European Council President, Donald Tusk, of the UK’s intention to invoke Article 50 of the Lisbon Treaty on March 29, 2017. Information available at <https://www.gov.uk/government/news/article-50-to-be-triggered-on-march-29> (last visited 24th of March 2017); see also, Statement by the European Council (Art. 50) on the UK notification, Brussels, 29 March 2017, available at http://europa.eu/rapid/press-release_STATEMENT-17-793_en.htm (last visited 29th of March 2017).
- ¹⁷⁶ See generally the Consolidated version of the Treaty on the Functioning of the European Union, available at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT&from=en> (last visited 24th of March 2017).
- ¹⁷⁷ See *supra* note 77, at 3.
- ¹⁷⁸ See Article 50 of the Treaty on European Union – Q&A, Timeframe Diagram, European Commission, official site, available at http://europa.eu/rapid/press-release_MEMO-17-648_en.htm (last visited 29th of March 2017).
- ¹⁷⁹ *Id.*
- ¹⁸⁰ *Id.* at 4.
- ¹⁸¹ The qualified majority is defined in this case as at least 72% of the members of the Council, comprising at least 65% of the population of the MSs (without the withdrawing state) (Article 238(3) b TFEU). *Id.*
- ¹⁸² See generally Phedon Nicolaidis, *Withdrawal from the European Union: A Typology of Effects*, 20 Maastricht Journal of European and Comparative Law 209, 218, (2013).
- ¹⁸³ See *supra*, Background Chapter.
- ¹⁸⁴ See Tim Oliver, *Europe Without Britain – Assessing the impact on the European Union of a British withdrawal*, Stiftung Wissenschaft und Politik, German Institute for International and Security Affairs,

- Berlin, September 2013, *available at* https://www.swp-berlin.org/fileadmin/contents/products/research_papers/2013_RP07_olv.pdf (last visited 24th of March 2017).
- ¹⁸⁵ *See supra*, Background Chapter, Pharmacovigilance Assessment.
- ¹⁸⁶ *See supra* note 89. *See also supra* Sub-Chapter, The Legal Consequences of the BREXIT Decision – Short Overview of Article 50 of TEU
- ¹⁸⁷ *Id.*
- ¹⁸⁸ EMA’s management board signed off on a budget of 322 million Euros for 2017, a 4.4% increase over 2016; *see generally* EMA Board Signs Off on 2017 Budget as Brexit Questions Linger, *available at* <http://raps.org/Regulatory-Focus/News/2016/12/19/26416/EMA-Board-Signs-Off-on-2017-Budget-as-Brexit-Questions-Linger/#sthash.cGkGdkqu.dpuf> (last visited 25th of March 2017).
- ¹⁸⁹ *Id.*
- ¹⁹⁰ *See supra* note 89, at 6.
- ¹⁹¹ *Id.*
- ¹⁹² *See generally* Bruno De Witte, Charles Grant, Jean-Claude Piris, United Kingdom’s Renegotiation of its Constitutional Relationship with the EU: Agenda, Priorities and Risks, EP Directorate-General for Internal Policies, Policy Department C, PE 536.489, December 2015, at page 30, *available at* [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/536489/IPOL_STU\(2015\)536489_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/536489/IPOL_STU(2015)536489_EN.pdf) (last visited 25th of March 2017).
- ¹⁹³ Although Article 50 TEU does not seem to be the right legal instrument to achieve the goal of such a “partial withdrawal,” with the state concerned remaining a Member State of the EU, not least because Article 50 adopts a ‘black or white’ approach. *Id.* at 19.
- ¹⁹⁴ *See supra* note 162.
- ¹⁹⁵ *See generally* Relocation of the European Medicines Agency – Copenhagen offers the optimal conditions, published by the Government of Denmark, *available at* <http://emacph.eu/EMAtocPH.pdf> (last visited 30th of March 2017).
- ¹⁹⁶ *Id.*
- ¹⁹⁷ *Id.*
- ¹⁹⁸ *Id.*
- ¹⁹⁹ *Id.* at 7.
- ²⁰⁰ *Id.*
- ²⁰¹ *Id.*
- ²⁰² *Id.*
- ²⁰³ *Id.* at 22.
- ²⁰⁴ *Id.*
- ²⁰⁵ *Id.* at 25.
- ²⁰⁶ *See* Brexit’s Impact on Healthcare and Life Sciences, *available at* <http://www.fticonsulting.com/~media/Files/emea--files/insights/articles/brexit-impact-healthcare.pdf> (last visited 29th of March 2017).
- ²⁰⁷ *See supra* note 117.
- ²⁰⁸ *Id.* at 2.
- ²⁰⁹ *Id.*
- ²¹⁰ *See* The impact of Brexit on the Health Care and Life Sciences Industries, *available at* <https://www.grantthornton.com/~media/content-page-files/advisory/pdfs/2016/brexit/Brexit-industry-update-HCLS-160711.ashx> (last visited 29th of March 2017).
- ²¹¹ *See* Impact of Brexit on life sciences and healthcare, *available at* <http://www.nortonrosefulbright.com/knowledge/publications/136982/impact-of-brexit-on-life-sciences-and-healthcare> (last visited 29th of March 2017).