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Assessing the impact of the disruption from the relocation of the European Medicines Agency

Final report

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Abbreviations

ADR	Adverse drug reaction
ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CRA	Charles River Associates
EBA	European Banking Authority
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
IT	Information technology
MA	Marketing authorisation
MS	Member States
NCAs	National Competent Authorities
OMP	Orphan Medicinal Product
PRAC	Pharmacovigilance Risk Assessment Committee
SMEs	Small and medium-sized enterprises

Executive Summary

Charles River Associates (CRA) was asked by EFPIA to conduct an evaluation of the impact of the potential disruption arising from the relocation of the European Medicines Agency (EMA) away from London to a new location in the European Union (EU). This report provides information to the industry on the risk to business continuity and the corresponding impact on public health (including patients and healthcare systems) resulting from the relocation of EMA

The EMA is a decentralised agency of the EU which evaluates and authorises medicinal products and has been housed in London's Canary Wharf since 1995. As the UK has notified the European Council of its intention to leave the Union, it is necessary to move EMA to another location within the Union's territory.¹

The purpose of this report is to consider, from an industry perspective, the potential risk to business continuity as a result of the relocation, in regard to the different activities of EMA as well as the corresponding impact on public health (including patients and healthcare systems). To determine the impact on the industry and knock-on impact on public health, we have used the evidence from academic literature and interviews.

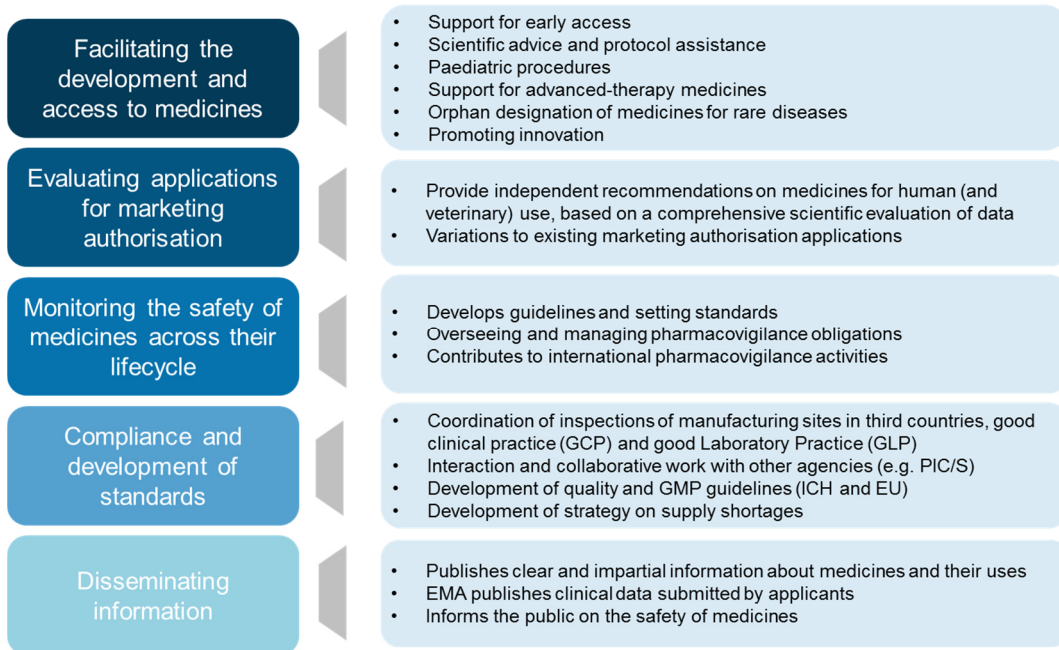
Overview of EMA activities

The EMA is responsible for protecting and promoting both public and animal health in 28 EU Member States, as well as in the countries of the European Economic Area (EEA), by ensuring that all medicines available on the EU market are safe, effective and of high quality. Our analysis, however, has focused on the activities of the EMA associated to human rather than animal health. EMA coordinates the evaluation and monitoring of centrally authorised products and national referrals, develops technical guidance and provides scientific advice to sponsors. EMA has an important coordinating role across the European Medicines Regulatory Network, and provides the administrative and scientific secretariat to all of the main scientific committees and working parties, giving the agency access to a pool of over 4,500 experts across the network.²

Figure 2 maps out the range of activities conducted by EMA. Based on EMA's clustering of these activities, these can be grouped into five categories, each containing sub-activities, as listed below.

¹ Council of the European Union (2017). Procedure leading up to a decision on the relocation of the European Medicines Agency and the European Banking Authority in the context of the UK's withdrawal from the Union, 22/06/2017, <http://www.consilium.europa.eu/en/press/press-releases/2017/06/22-euco-agencies-relocation/>

² EMA Annual Report 2016

Figure 1: List of EMA activities by group

Source: Developed from the description of activities by European Medicines Agency³

There are two significant ways that relocation could impact on the activities of EMA. Firstly, the location of EMA could impact its ability to coordinate the network of expertise and to call on expertise. Secondly, the relocation could jeopardise the EMA's ability to retain its own capabilities, affecting its contribution to the process. Based on input from regulatory experts, we have largely focused this report on the ability of EMA to retain the key staff to perform their activities.

For each of EMA's five key activities, CRA has identified the risk of disruption by assessing the importance of EMA internal expertise. We have used two approaches to collect qualitative and quantitative data on this:

1. Review EMA staff involved in activities and the types of skills that are vital to performing these activities, together with volume and timelines for processing
2. Interview regulatory experts, capturing their perspectives on the impact of relocation

Impact of EMA relocation on risk of business discontinuity

This section of the report takes into account the role that EMA plays within each group of activities presented above, the level of human and capital resources associated to this, and the level of expertise and experience involved in conducting EMA's operations.

We first mapped the processes and activities to the departments within EMA that carry them out. We then drew on interviews with regulatory experts to determine how interchangeable these resources are, as well as to what extent these roles can be backfilled through secondments or new hires. This provided us with a risk of discontinuity.

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European Medicines Agency – Website: About Us: What we do. Accessible at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42

Next, we considered the impact of these activities on the pharmaceutical industry and, subsequently, their impact on public health (this can be described as a chain of causality). The premise is that loss of staff and other resource constraints can impact efficiency and business continuity, which in turn can have implications for both patients and industry; for example, if there is a delay in marketing authorisation (MA), this delays the marketing of a new product and can impact patients by delaying their access to medicines.

As highlighted in Table 2, according to our analysis, two areas of activity have the greatest risk of disruption due to the relocation of EMA, these include:

- EMA's evaluation of applications for MA,
- Post-marketing activities, particularly pharmacovigilance.

Any disruption to these activities are likely to have direct implications for patients unless they are adequately prioritised and contingency staff (seconded national experts) are provided.

Failure to ensure adequate staff in these areas could mean that EMA is not able to abide by the legal procedural timelines – or “timeouts” are used inappropriately. This could lead to delays in patient access to new life-saving therapies and a potential dysfunctioning in the coordination of pharmacovigilance activity. This would mean that when adverse effects and toxicity occur, such information may not be analysed and communicated effectively across the European network and this could lead to a slower reaction to the monitoring, detection and assessment of adverse drug reactions (ADRs) across Member States.

Disruption to some activities could have knock-on effects on other activities. This is the case, for example, for the paediatric department, because of the role of the paediatric investigation plan (PIP) in MA, and disruption of which may impact the MA process. Additionally, the workload in some departments may increase as a result of Brexit, such as MA variations or a requirement for new site inspections, which also has implications on business continuity.

We find the other three areas of activity have less of a direct impact on business continuity or public health. However, a significant concern is that activities that are important in the medium term may be neglected. The result of this would be that Europe “falls behind” the rest of the world in terms of regulatory science; there is especially concern about falling behind Japan and the US. This could have a particular impact on investments into the European market and in particular the growth prospects of small and medium-sized enterprises (SMEs).

Table 1: Ranking of activities by their level of risk of disruption and impact on business continuity and public health

	Risk of disruption and impact on business continuity	Impact on public health
Evaluating applications for marketing authorisation	Loss of expertise and procedural experience in this area would lead to a significant level of disruption to EMA's ability to coordinate the CHMP and could jeopardise the entire MA process	This would result in a direct impact on patients' ability to have timely access to new treatments
Monitoring the safety of medicines across their lifecycle	Risk of disruption in this area is high, due to management of the IT systems and the high volume of safety signals across the network	This disruption may impact critical safety functions of the EMA and lead to delays in the identification, management and communication of product safety issues
Facilitating the development and access to medicines	There is a moderate risk of disruption in this sector. Some areas directly link to the longer-term marketing authorisation process. In other cases, the damage is on longer-term EU competitiveness	This would not result in direct impact on patients in the short-term. However, this could have a knock on effect on other parts of the regulatory process and on long-term incentives to innovate
Compliance & development of standards	This area has a lower risk of disruption as the activities require fewer EMA resources. However, some scientific and regulatory expertise, such as the coordination of inspections or the involvement in ICH are an essential support function	This would have less of an immediate effect on the public compared to the previous activities
Disseminating information	Whilst these activities are completely dependent on EMA staff, this segment is based on reports already generated through other EMA activities, and has the least potential to cause problems with business discontinuity	Many stakeholders would regard the dissemination of information very useful in driving standards and meeting regulatory requirements, but is not critical in terms of public health

High impact on public health

Medium impact on public health

Low impact on public health

Source: CRA analysis

1. Introduction

Charles River Associates (CRA) was asked by EFPIA to conduct an evaluation of the impact of the potential disruption arising from the relocation of the European Medicines Agency (EMA) away from London to a new location in the EU. This report provides information to the industry on the risk to business continuity and the corresponding impact on public health (including patients and healthcare systems) resulting from the relocation of EMA

1.1. Background

The European Medicines Agency is a decentralised European Union (EU) body which evaluates and authorises medicinal products within the EU and the European Economic Area (EEA) and has been housed in London's Canary Wharf since 1995. It is responsible for coordinating scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products for human and veterinary use.⁴

As the United Kingdom (UK) has notified the European Council under Article 50 of the Treaty on European Union of its intention to leave the Union, it is necessary to move EMA to another location within the Union's territory.⁵ At the European Council (Art. 50) on 29 April 2017, the EU institutions outlined their intention to work out a transparent procedure that should ensure that a decision can be taken on the new seats of the decentralised agencies – EMA and the European Banking Authority (EBA) – in the autumn of 2017. The procedure for the relocation of the agencies was endorsed in the margins of the European Council (Art. 50) in June and a final decision should be reached on 20 November 2017.

The purpose of this report is to consider from the industry perspective the potential risk to business continuity resulting from relocation of the different activities of EMA, as well as the corresponding impact on public health (including on patients and healthcare systems). This will serve to provide decision makers additional considerations from a pharmaceutical industry perspective on the decision about where to relocate the EMA, and avoid any arbitrary decisions that could lead to being located in a country that would jeopardise its activities and, in turn, compromise companies' ability to deliver safe and effective medicines to patients.

1.2. Methodology

As set out above, this research seeks to provide information on the risk to business continuity and the corresponding impact on public health. This analysis starts with a review of how EMA works today and then considers the factors that affect the risk to business continuity and its impact on the pharmaceutical industry and, subsequently, the impact on public health (this can be described as a chain of causality). To do this, we reviewed the existing literature on the operations of EMA (especially from EMA itself but also drawing on the academic and grey literature – a total of 20 publications) to understand how it works today, and we mapped out its key activities and the role of internal EMA staff versus experts from Member States.

We developed a set of hypotheses about the potential impact of disruption to EMA's activities for the industry and tested these through a series of interviews with regulatory and business experts. Interviews were conducted with experts from GSK, Pfizer, MSD, and Sanofi, and

4 EMA (2017) "About us", accessible at:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/08/WC500211862.pdf

5 "Procedure leading up to a decision on the relocation of the European Medicines Agency and the European Banking Authority in the context of the United Kingdom's withdrawal from the Union"
www.consilium.europa.eu/en/meetings/european.../22-euco-procedure-agencies_pdf/

wider comments were provided by EFPIA Regulatory Committee. Recently, EMA itself has published its plan for ensuring that disruption is minimised.⁶ We have not taken this into account in our assessment of risk of disruption but compare the priorities set out by the EMA against the results of our analysis.

1.3. The structure of the report

The rest of the report is structured as follows:

- In Chapter 2, we set out the role of EMA and the framework for considering the risk to business continuity.
- In Chapter 3, we review the activities of EMA and prioritise them in terms of risk to business continuity.

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“EMA prepares for Brexit” Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002789.jsp&mid=W0b01ac058004d5c1

2. Overview of EMA activities

To assess the risk of disruption from relocation, we need to start from how EMA works today and then consider what could happen following relocation.

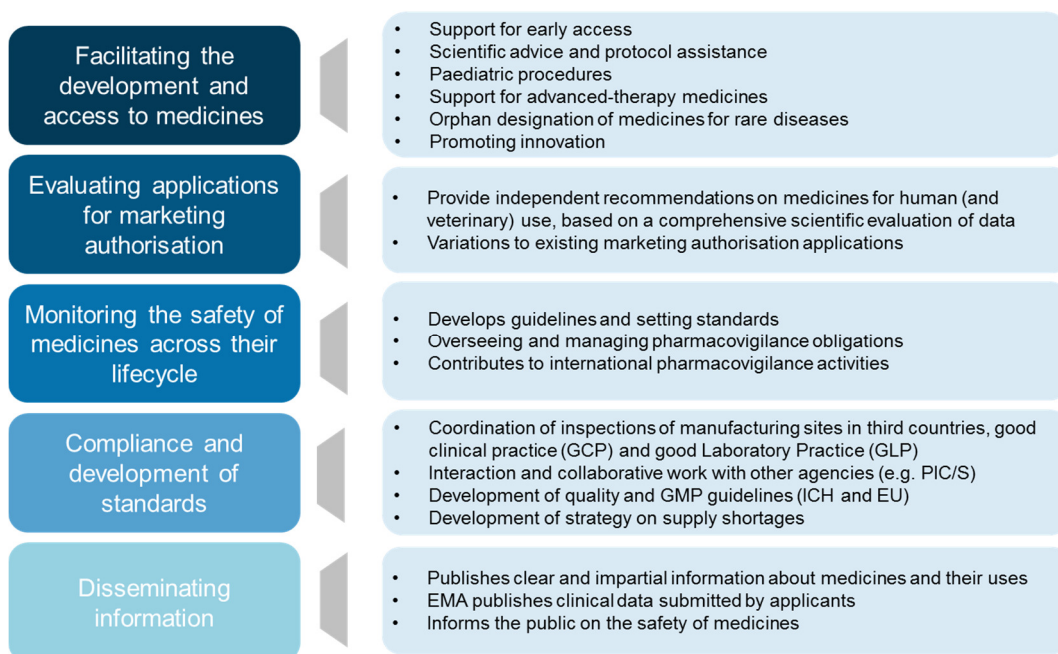
2.1. Overview of EMA activities

The EMA has responsibility for the protection and promotion of public and animal health in 28 EU Member States, as well as in the countries of the EEA, by ensuring that all medicines available on the EU market are safe, effective and of high quality. Given our focus on human health, the analysis has focused on the activities of the EMA associated to human rather than animal health.

2.2. What EMA does

EMA coordinates the evaluation and monitoring of centrally authorised products and national referrals, developing technical guidance and providing scientific advice to sponsors. Its scientific assessment of medicines is undertaken via a network of experts across the EU, drawing on resources of National Competent Authorities (NCAs) of EU Member States. Figure 2 maps out the range of activities conducted by EMA. Based on EMA's clustering of these activities, they can be grouped into five categories, each containing sub-activities, as listed below.

Figure 2: List of EMA activities by group



Source: Developed from the description of activities by European Medicines Agency⁷

⁷

European Medicines Agency – Website: About Us: What we do. Accessible at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42

2.3. Business continuity risks

In order to identify which of these fields of activities are most likely to be impacted by disruptions, we consider some of the factors that are likely to cause disruptions. There are two significant ways that relocation could impact on the activities of EMA. Firstly, the location of EMA could determine its ability to coordinate the network of expertise and its ability to call on expertise. Secondly, the relocation could jeopardise the EMA's ability to retain its own capabilities, affecting its contribution to the process.

2.3.1. Coordinating the network and the capabilities of the host country

One possibility is that the location is important as it allows physical proximity to expertise in the host country. EMA has a series of core committees that are responsible for its activities. Focusing on human medicines, these include the Committee for Medicinal Products for Human Use (CHMP), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Pharmacovigilance Risk Assessment Committee (PRAC) and Committee for Advanced Therapies (CAT). Relocation could have an impact on these committees' activities.

EMA has an important coordinating role across the European Medicines Regulatory Network, and provides the administrative and scientific secretariat to all of the main scientific committees and working parties, giving the agency access to a pool of over 4,500 experts across the network.⁸ Therefore the coordination of this network not only requires accessibility, but the support of EMA staff.

Interviews with regulatory experts indicated they were in strong agreement that EMA works as a decentralised agency using a network of experts from across the EU. The availability of expertise from the network does not depend on the proximity of external experts (i.e. academics), national regulatory agency experts or industry or patient representatives. This was not a factor affecting EMA's operation. Thus, external expertise could be flown in to EMA's new location (provided it had sufficiently good transport connections) if and when required, and that this would not cause disruption to the system. The importance of the local NCAs and local industry as a source of expertise was therefore discounted as a risk to business continuity.

2.3.2. The role of EMA's staff and internal capability

The second risk is retention of the EMA's internal capability. EMA staff support its activities including administrative and procedural aspects of EU law related to the evaluation and safety-monitoring of medicines in the EU. As of December 2016, the staff numbered 897 men and women, working across 7 divisions as well as other support functions, as shown in Figure 3 below.

The interviews with regulatory experts indicated that although EMA staff do not necessarily undertake all of the activities – for example, the assessment of application for marketing authorisation (MA) – their key role is coordinating the network of expertise and ensuring that the specific EU procedures under EMA's responsibility are followed. The workload of EMA staff requires a lot of very skilled scientific administrators and secretariats to help organise and coordinate the process. This involves accessing necessary external expertise.

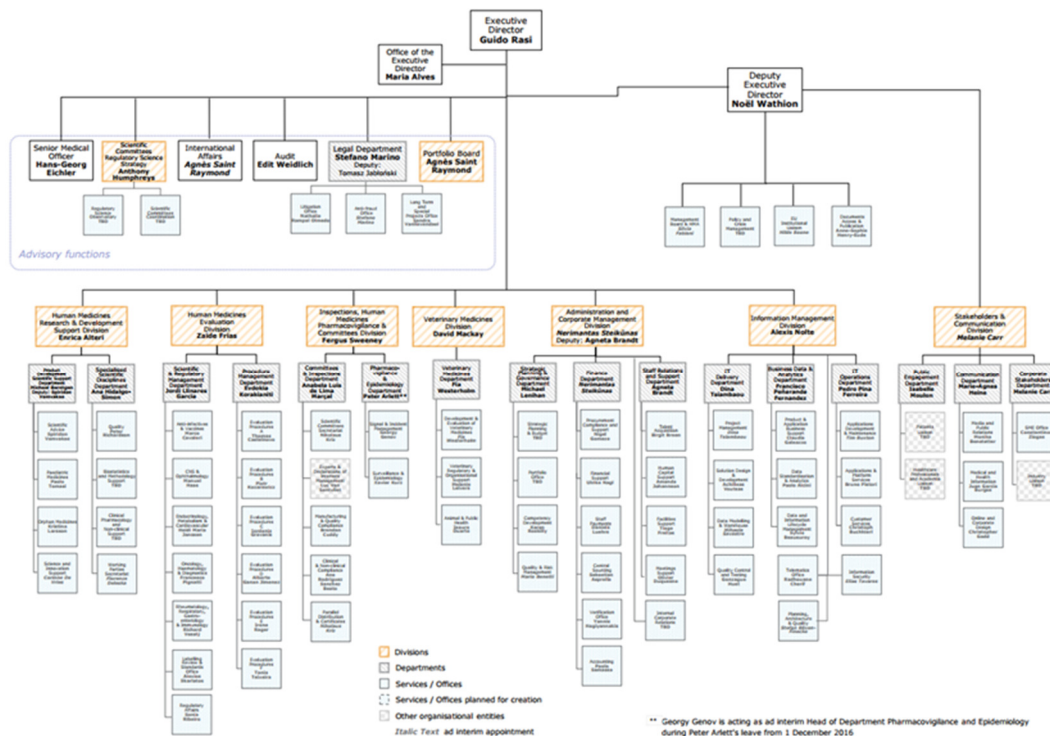
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EMA Annual Report 2016

All interviews have reported that “scarce” staff – those key to activities and difficult to replace – are those with:

- Scientific and medical expertise
- Experience with EMA processes and regulatory procedures

Figure 3: EMA organisation chart



Source: European Medicines Agency

It is therefore the premise of this analysis that EMA’s ability to retain or attract highly competent staff and internal subject matter experts to manage the central regulatory system is the primary factor in assessing the potential for disruption. This forms the backbone of all activities, and if this is majorly disrupted then this can impact the completion of tasks.

IT infrastructure

EMA’s information technology (IT) capacity is important in terms of sharing and communicating information. A lot of activities are dependent on these resources, such as the EudraVigilance database for pharmacovigilance. In the interviews there arose some concerns relating to risks from relocation. In particular, it was noted that EMA’s current technology platform relies on a server-based system rather than cloud-based services, with the result that relocation has risk in terms of business continuity. One key consideration would therefore be the portability of EMA IT systems.⁹ However, the interviewees agreed it is unaffected by the relocation destination per se, providing the process is appropriately managed and there is limited impact from staff resource constraints. The opportunity to contract out for IT expertise and capability is possible in all countries in the EU – this was therefore seen as a relatively low consideration in the decision of where to relocate.

9 Interview with regulatory expert

Given the structure of EMA and our concern for public health, the analysis has focused on the potential disruption linked to relocation of EMA staff to a new location.

2.4. A framework for assessing the risk to continuity

For each of EMA's five key activities, CRA has identified the risk of disruption by assessing the importance of EMA internal expertise. We have used two approaches to collect qualitative and quantitative data on this:

3. Review EMA staff involved in activities:
 - Use the EMA organisation chart to map to activities
 - Review the professional background of "experts"
 - Assess whether experts are attracted to the local market
4. Interview regulatory experts, capturing their perspective on the impact of relocation by asking the following questions:
 - What activities are the most reliant on support from EMA staff?
 - Which of these activities rely the most on scientific and medical experts at EMA?
 - Which types of internal scientific and medical experts are going to be most difficult to retain?
 - What impact does each activity have on other EMA activities?

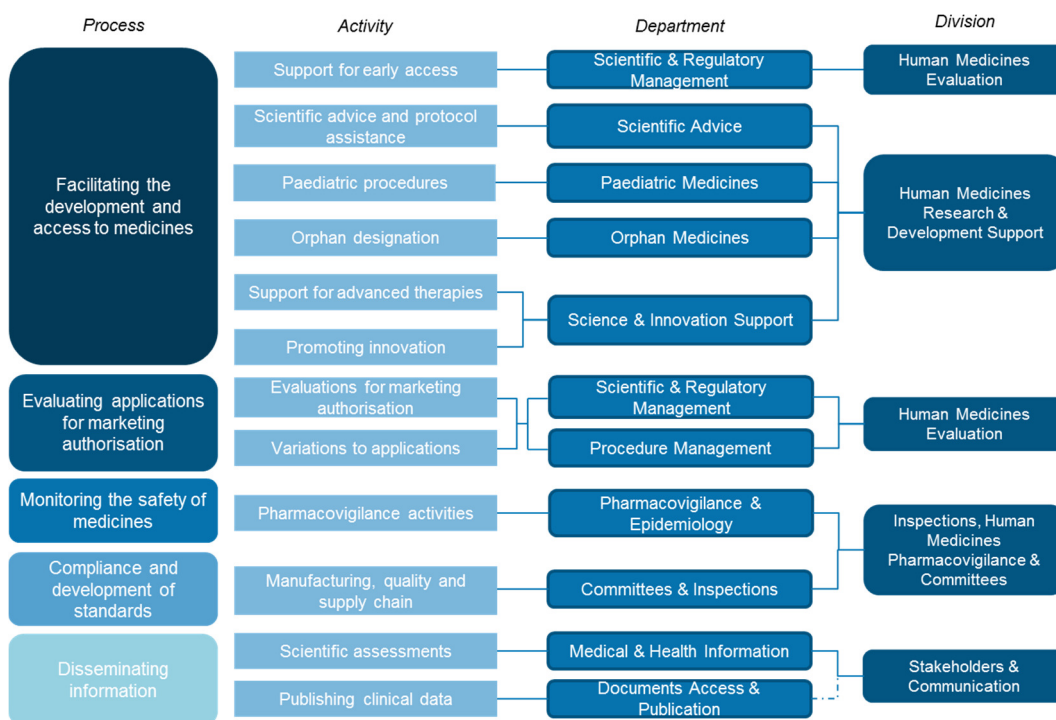
To assess the impact on the industry and knock-on impact on public health, we have used the evidence from academic literature and interviews.

3. Impact of EMA relocation on risk of business discontinuity

This section considers the role that EMA plays within each group of activities presented in section 2.2, and the level of the activity based on the 2016 annual report, but also the level of expertise and experience involved in conducting EMA's operations.

The first step was to map the processes and activities to department within EMA, as shown in Figure 4 below.

Figure 4: Mapping activities to EMA's organisation chart



Source: CRA analysis

We then drew on interviews with regulatory experts to determine how interchangeable these resources are, as well as to what extent these roles can be backfilled through secondments or new hires. This provided us with an estimated risk of discontinuity. Next, we considered the roles of these activities and the impact on the pharmaceutical industry and, subsequently, the impact on public health (this can be described as a chain of causality). The premise is that loss of staff and other resource constraints can impact efficiency and business continuity, which in turn can have implications for both patients and industry; for example, if there is a delay in MA, this delays the marketing of a new product and impact patients through delays in getting access to medicines.

3.1. Facilitating the development of and access to medicines

The EMA plays a vital role in supporting medicine development for the benefit of patients and also seeks to foster patients' early access to new medicines that address public health needs. The Agency uses a wide range of regulatory mechanisms to achieve these aims:

- Support for early access
- Scientific advice and protocol assistance
- Paediatric procedures

- Scientific support for advanced-therapy medicines
- Orphan designation of medicines for rare diseases
- Scientific guidelines on requirements for testing the quality, safety and efficacy of medicines
- The Innovation Task Force

Generally these processes are high volume, short procedures, thus a drop in staffing levels would lead to disruption and impact EMA's ability to process applications in the short-term. During 2016, together with the relevant committees, EMA reviewed 549 paediatric investigation plans (PIPs) and 329 applications for orphan designation.¹⁰ EMA staff play a key role in assessing and coordinating these activities. In some areas, the teams are small and this make them particularly reliant on a small number of experts with procedural and scientific expertise. It has been argued that losing staff in these areas could lead to a higher level of disruption.¹¹

EMA's in-house experts who coordinate the provision of scientific advice have more general scientific understanding. In 2016 EMA finalised 439 requests for scientific advice and 122 requests for protocol assistance.¹² These are very high volume and rapid turnover procedures, and the delivery could be severely compromised in the event of staff losses. Additionally, the experience of the overall MA process that will subsequently be applied to the medicines is vitally important, making staff expertise regarding the regulation and the internal processes key to this activity.

Impact on business continuity and on public health

All of the activities within this group are important functions of EMA, but some activities are arguably more critical to business continuity in the short and medium term.

- The paediatric procedures result in authorisation of a PIP, which is a necessary condition for getting a marketing authorisation.¹³ The risk of disruption to business continuity is therefore high as the inability to process compliance checks may act as a roadblock for other processes. This could have further implications on industry through delaying development of new medicines and initiation of clinical trials.
- Scientific advice is intended to ensure that developers perform the appropriate tests and studies in patients in order to collect robust high-quality data for the MA application. There is evidence that this improves the MA process¹⁴, but there are no legal requirements for this activity. Disruption to EMA's ability to deliver scientific advice increases probability of non-compliance with regulatory requirements when applying for MA or extension of

¹⁰ EMA Annual Report 2016

¹¹ Interview with regulatory experts.

¹² EMA Annual Report 2016

¹³ All applications for MA for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000608.jsp&

¹⁴ For early scientific advice by regulatory, analysis has shown that products undertaking early scientific advice have higher probability of achieving regulatory approval. See for example "Deerfield Institute – EuropaBio Report on Regulatory and HTA scientific advice for small and medium enterprises", March 2015.

indication. There is also the likelihood for implications much further down the line (e.g. knock-on effects within the MA process) and this can lead to delays in processing the MA.

- The process for assigning an orphan medicine designation (which typically occurs some years before MA) or advanced therapy designation is likely to have a smaller impact on business continuity. These are often not a business critical activity and would not be a roadblock in the approval process. However, they are important for some companies such small and medium-sized enterprises (SMEs) in terms of driving a business case for development and access to finance.¹⁵

- PRIME enables early dialogue and accelerated assessment of promising new medicines that have the potential to address patients' unmet needs and entry points for this is prior to initiation of confirmatory trials.¹⁶ If EMA is unable to adequately resource PRIME, companies could miss the window of opportunity to apply for PRIME. Additionally, disruption to EMA's support around early access programmes (PRIME, Adaptive Pathways) may in the long term reduce the competitiveness of the EMA and the EU regulatory system as a whole. These schemes are important in ensuring Europe remains advanced in terms of regulatory science.¹⁷

A significant concern is that Europe will fall behind Japan and the US and the rest of the world in terms of regulatory science. Regulatory predictability is important to all companies but particularly SMEs involved in biotech product development and this is likely to have a long-term impact on incentives to innovate.

There is a risk of disruption in this activity. This will not result in direct impact on patients, however there may be delays in development of medicines that could have global implications. Additionally there may be knock-on effects on other parts of the regulatory process and on long-term incentives to innovate as well as the overall competitiveness of the EU regulatory system (e.g. impact on SMEs).

3.2. Evaluating applications for marketing authorisation

EMA's scientific committees provide independent recommendations on medicines for human and veterinary use, based on a comprehensive scientific evaluation of data.¹⁸ The EMA coordinates CHMP in its scientific evaluation of new treatments, with input from various other internal committees. The CHMP also establishes Scientific Advisory Groups (SAGs) to provide advice in connection with the evaluation of specific types of medicines or treatments. These committees consists of independent experts from each of the 28 Member States. While the initial assessment reports are written by the Rapporteur and other committee members (within the national agencies), EMA's in-house scientific experts act as coordinators and project managers (coordinating the activities of national experts and providing assistance in drafting

15 Miller, K. L. (2017). 'Do investors value the FDA orphan drug designation?', *Orphanet Journal of Rare Diseases*, 12(1): 114.

16 Jordi Llinares and Zahra Hanaizi (2016) "Regulatory brief on new PRIME scheme", 3 October 2016

17 "EMA Launches its own Fast Track for Breakthrough Therapies, from the Clinic" Denise Neves Gameiro, 9 March 2016.

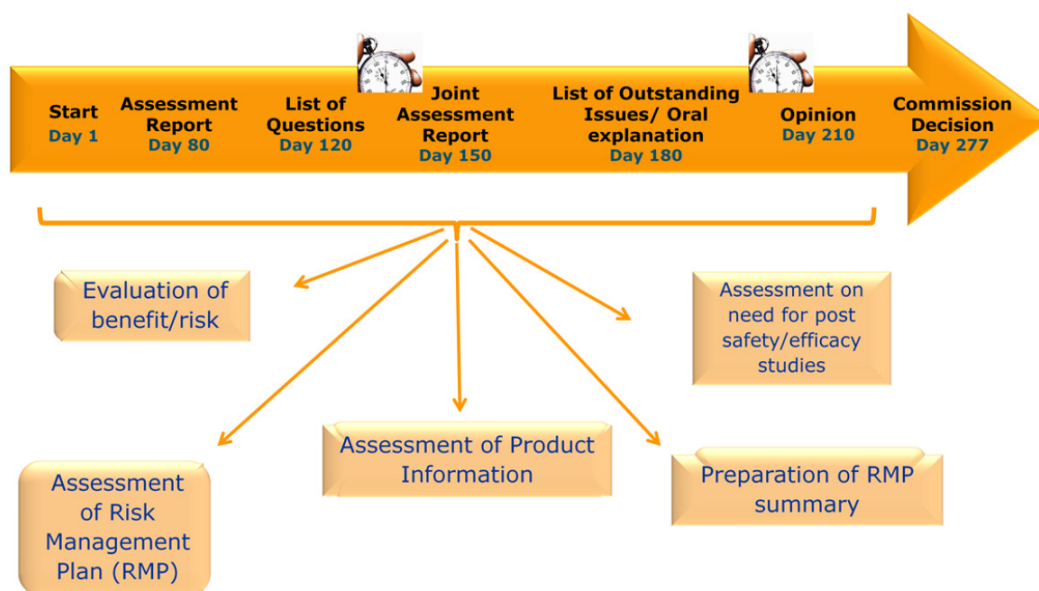
18 European Medicines Agency (2017) About Us: What we do ; http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42

the report). If the CHMP is not coordinated effectively by EMA due to staff losses, this could delay CHMP recommendations on MA.

Industry experts reported that EMA's scientific administrators largely bring the procedural expertise and regulatory knowledge that are used across tasks, as the scientific expertise mainly comes from Member States. More importantly, they coordinate the expertise amongst the assessors and ensure compliance with procedures (in line with EU regulation) and make sure the process is conducted efficiently. As illustrate in Figure 5, the level of scientific expertise is also needed as a prerequisite for carrying out this role. The combination of scientific and medical specialists (oncology, endocrinology etc.) combined with the regulatory knowledge is critical in this activity. In fact, the Human Medicines Evaluation Division is the largest in terms of staff numbers at EMA.

As illustrated in Figure 5, assessing an application for a new medicine can take up to 210 'active' days. In 2016 there were 85 MAA pre-submission meetings, 114 initial MAs and 6,204 post-authorisation application variations (including line extensions, Type IB, Type II and Type IA variations).¹⁹

Figure 5: EMA timeline of assessment of an application for marketing authorisation



Source: European Medicines Agency²⁰

In case of loss of staff, hiring new scientific in-house experts (without understanding of the science or regulatory requirements) would slow down the operative efficiency of the MA process. In terms of redeveloping these competencies, one regulatory expert suggested that it would take approximately 1-2 years for new specialised staff to become fully confident in terms of the regulatory and procedural requirements. The most likely source for backfilling these positions is from NCAs, who would be aware of the EMA process through their involvement as national experts in the process. Hiring from the industry has constraints due to

¹⁹ EMA Annual Report 2016

²⁰ European Medicines Agency (2017) Overview of the centralised procedure at the European Medicines Agency http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/02/WC500201043.pdf

EMA's conflict of interest policy, for example it is not possible to work on a submission from the company that an industry expert has left for a period of time.

Impact on business continuity and on public health

EMA's evaluations of MA applications (submitted through the centralised procedure) provide the basis for the authorisation of medicines in Europe. A high proportion of EMA staff work in this area and have the necessary scientific and procedural expertise. Any potential loss of such combined experience may lead to ineffective coordination of the assessments, and lack of compliance with procedures (in line with EU regulation), and this could significantly disrupt the entire MA approval process. It is a requirement of the MA process that an opinion is provided in 210 days.²¹

Such disruption, both in terms of volume of staff required and the level of expertise, is likely to have a significant impact on the overall MA evaluation process. This could mean failure to abide by the legal procedural timelines or lead to procedural delays in approving new medicines across Europe.

There are also issues surrounding maintenance. The inability to maintain the pace of the MA process in the EU will raise compliance issues for companies. This could lead to delays in communicating safety issues and updating product information. There will also need to be process variations to updates MAs in relation to the UK's withdrawal from the EU, which needs to be factored in the level of activity required.

The evaluation of MAs is also critical to ensure that Europe has a competitive assessment internationally. EMA provides the structure, guidance and coordination in order to carry out the operations. On average, the EMA takes around six months longer than the FDA to approve a new drug or a new indication for a medicine.²² This in turn could lead to further delays in patient access to new life-saving treatments.

The risk of disruption is significant in this area. The loss of expertise and regulatory experience in this area could jeopardise the entire MA process. The impact to this area could be exacerbated should there be high level of staff loss combined with an increase in industry submissions to changed MAs. This will in turn result in a direct impact on patients' ability to have timely access to new treatments.

3.3. Monitoring the safety of medicines across their life cycles

EMA, in cooperation with member state competent authorities, has the responsibility for maintaining the risk-based programme for routine pharmacovigilance inspections of holders of MAs for centrally authorised products and ensuring its implementation. EMA also plays a key role in the coordination of pharmacovigilance inspections specifically triggered by CHMP and in inspection follow-up.

²¹ "Overview of Authorisation Procedures for Medicinal Products"
http://www.raps.org/uploadedFiles/PDF_Assets/EU%20Fundamentals,%20Ch.%2017.pdf

²² Beishon, M. (2014) "Approval rating: how do the EMA and FDA compare?" *Cancer World*, available at <http://www.cancerworld.org/Articles/Issues/58/January-February-2014/Cutting-Edge/637/Approval-rating-how-do-the-EMA-and-FDA-compare.html>

The role of EMA has changed over the last five years. The introduction of the Pharmacovigilance Legislation, in 2012, established PRAC.²³ This led to a clarification of the roles and responsibilities of those involved in monitoring the safety and efficacy of medicines in Europe and strengthened coordination and the role of EMA, leading to more robust and rapid EU decision-making.

Overall, in this area, PRAC (composed of national experts) is central to the process. However, EMA staff coordinates the monitoring of pharmaceutical companies' compliance with their pharmacovigilance obligations.²⁴ EMA's in-house experts need sufficient scientific and medical understanding to process the information correctly, as well as the regulatory experience. If there is a safety signal, they are responsible for ensuring that the necessary process in response to the safety issue is followed, and in 2016 alone EMA reviewed 2,372 safety signals.²⁵

The reporting and communication of information on safety issues is important, and EMA provides the link to international databases on a global level. The IT infrastructure is therefore an important component of the system, as are the staff who are able to query the database accordingly based on the scientific and epidemiology requirements.

Impact on business continuity and on public health

Pharmacovigilance is one of the key responsibilities of EMA in terms of safeguarding public health. Significant loss of scientific expertise and IT staff could have repercussions on key activities such as the evaluation of safety signals and management of the EudraVigilance database, for example.

Some activities of EMA are also heavily reliant on IT infrastructure, such as EudraVigilance for pharmacovigilance. One key consideration is the portability of EMA IT systems and ensuring that EMA has enough resources to manage this during the transition.

The pharmacovigilance activities and MA activities are interrelated. The consequences of this monitoring may also be impeded as a result of delays to evaluations (loss of staff), as it is important to consider some pharmacovigilance activities are post-authorisation monitoring.

Disruption to pharmacovigilance activities could have a direct impact on public health, as the European Medicines Regulatory Network may not have the most up-to-date information on a medicine's benefits and risks, leading to delays in addressing safety issues.

There is a risk of disruption arising from the management of the IT systems and the management of safety signals across the network if key staff are lost. This disruption may impact critical safety functions of the EMA and lead to delays in the identification, management and communication of product safety issues

3.4. Compliance and development of standards

The EMA is responsible for harmonising standards set out in EU legislation and guidelines for good clinical practice (GCP), good laboratory practice (GLP) and good manufacturing practice

²³ European Medicines Agency (2012) Press release: New pharmacovigilance legislation comes into operation. Better protection of public health through strengthened EU system for medicines safety. Accessible at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/07/WC500129311.pdf

²⁴ Interview with EFPIA regulatory expert

²⁵ EMA Annual Report 2016

(GMP) for investigational medicinal products.²⁶ In practice, the responsibility for the inspections regime for manufacturing is handled by Member States; however, EMA has a coordinating role for GMP inspections of manufacturing sites for medicines and develops quality and GMP guidelines (in the EU, and coordinates with other regions through the International Conference on Harmonisation, ICH). IT capacity and system management is also very important within this area, such as monitoring EudraCT and EudraGMP.²⁷

In 2016 there were 181 notifications of suspected quality defects and 3,787 certificate requests, of which 487 were urgent requests.²⁸ If these cannot be processed timely then they can have a knock-on effect that impacts patient's access to safe medicines.

The administrative functions include the Scientific Committees Secretariat, which coordinates the European network of experts across activities. EMA's Committees and Inspections Department, which is primarily to do with compliance, has a relatively high proportion of administrative functions. Activities within this department have a greater reliance on staff with scientific and regulatory expertise, such as manufacturing and quality compliance (for GMP inspections) and clinical & non-clinical compliance (for GCP inspections). These are both essential support functions when issues are identified across the European network.

Impact on business continuity and on public health

Overall this activity is reliant on fewer EMA resources and is has less direct impact on patients when compared to the activities previously discussed. However, it is important to consider how activities in this area can have an impact on others processes. The coordination of EMA's committees forms the backbone for key decisions and the Agency's scientific opinions.

In addition, coordination of inspections has implications for the timing of MA submissions. The coordination of quality defect reports is an important activity for industry to manage batch recall where necessary, as this is essential to safeguard public health.

From a European public health strategy perspective, it is important for Europe to engage in international activities, such as ICH. Without this, global initiatives would be led by the priorities of other regions (in particular, Japan and the US), and Europe's voice would inevitably be given less priority.

This activity requires fewer EMA resources, and therefore the risk of disruptions is relatively lower. However, some scientific and regulatory expertise, such as the coordination of GMP and GCP inspections or the involvement in ICH are an essential support function. This will have less impact on the immediate public compared to the previously discussed activities.

3.5. Disseminating information

EMA publishes information about medicines and their uses as well as guidelines for patients and healthcare professionals. This includes public versions of scientific assessment reports (EPARs), review of patient information leaflets and Summary of Product Characteristics. EMA

²⁶ European Medicines Agency Website - Research and development: Compliance, accessible at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001794.jsp&mid=WC0b01ac0580b95063

²⁷ Interview with EFPIA regulatory expert

²⁸ EMA Annual Report 2016

also publishes clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure.

The level of activity is high. For example, if we look at the last year, EMA published 71 guidelines and concept papers adopted by CHMP in 2016, and 82 publications by EMA staff members.²⁹ All these activities are completely dependent on EMA staff and are associated with some scientific and procedural expertise. However, the output in this segment is based on reports already generated through other EMA activities (e.g. MA activity, or facilitating the development of and access to medicines).

The role of EMA staff in this segment largely consists of communication specialists, medical writers, legal and web management expertise. As a result, a large proportion of the EMA staff act in a secretarial capacity – including preparation of product related information for the general public, such as EPAR summaries and safety communications. Management of Early Notification System includes development and distribution of aligned positions of regulatory authorities across the EU. This division is also very important for managing EMA's interaction with patients, consumer organisations and industry.

Impact on business continuity and on public health

This activity has the least potential to cause problems with business discontinuity, however many stakeholders would regard the dissemination of information as highly important for public health.

3.6. Impact on business continuity for industry

In the previous sections, we have set out the risk of disruption and the impact on business continuity within the industry and any corresponding impact on patients. However, we have not taken into account the actions undertaken by EMA to mitigate any disruption.

EMA's business continuity plan

EMA has developed and initiated a business continuity plan to deal with the uncertainty and workload implications linked to the UK's withdrawal from the EU and EMA's relocation.³⁰ This provides some indication of which activities it will seek to prioritise, as follows:

- **Category 1**, includes the highest priority activities: assessment and safety monitoring of medicines; the infrastructure of the European regulatory system for medicines, including for example the coordination of actions to protect the safety of patients in all EU Member States, inspections across the EU or maintenance of the functionality and security of critical IT applications used by all Member States.
- **Category 2**, includes activities with the second highest priority: the proactive publication of clinical data, and various initiatives that aim to promote availability of medicines as well as some political priorities of the EU, for example EMA's contribution to the fight against antimicrobial resistance or the Agency's interactions with Health Technology Assessment (HTA) bodies.

²⁹ European Medicines Agency - Annexes to the annual report of the European Medicines Agency 2016 http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2017/05/WC500227333.pdf

³⁰ European Medicines Agency (2017) Press release: EMA prepares for Brexit Business continuity plan aims to preserve Agency's ability to protect public and animal health; accessible at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/08/WC500232808.pdf

- **Category 3**, includes the lowest priority activities: the development of the European Medicines Web Portal, a new publicly available online information source on all medicines marketed in the EU; EMA's contribution to the e-submission project; the development of a transparency roadmap; participation in the benchmarking of medicines regulatory authorities in the EU as of 2018.

Impact of disruption on business continuity and public health

EMA's business continuity plan is mostly consistent with areas that are most impacted according to our analysis as summarised below. As highlighted in Table 2, according to our analysis, two areas of activity have the greatest risk of disruption due to the relocation of EMA, these include:

- EMA's evaluation of applications for MA,
- Post-marketing activities, namely pharmacovigilance.

Any disruption to these activities are likely to have direct implications for patients unless they are adequately prioritised and contingency staff (seconded national experts) are provided where necessary.

Failure to ensure adequate staff in these areas could mean that EMA is not able to abide by the legal procedural timelines – or “timeouts” are used inappropriately. This could lead to delays in patient access to new life-saving therapies and a potential dysfunctioning in the coordination of pharmacovigilance activity.

This would mean that when adverse effects and toxicity appear, such information may not be analysed and communicated effectively across the European network, and this could lead to a slower reaction to monitoring, detection and assessment of adverse drug reaction (ADRs) across Member States.

Disruption in some activities could have knock-on effect on other activities. This is the case, for example, for the paediatric department, because of the role of the paediatric investigation plan (PIP) in MA, and disruption of which may impact the MA process. Additionally, the workload in some departments may increase as a result of Brexit, such as MA variations or a requirement for new site inspections, which also has implications on business continuity.

IT capacity is very important, and this is a potentially fragile part of the Agency because a lot of activities are dependent on these resources. However, the risk is related to transition management rather than the relocation destination.

A significant concern is that activities that are important in the medium term may be neglected. The result of this would be that Europe “falls behind” the rest of the world in terms of regulatory science; there is especially concern about falling behind Japan and the US. This could have a particular impact on investments into the European market.

Table 2: Ranking of activities by their level of risk of disruption & impact on business continuity and public health

	Risk of disruption and impact on business continuity	Impact on public health
Evaluating applications for marketing authorisation	Loss of expertise and procedural experience in this area would lead to a significant level of disruption to EMA's ability to coordinate the CHMP and could jeopardise the entire MA process	This would result in a direct impact on patients' ability to have timely access to new treatments
Monitoring the safety of medicines across their lifecycle	Risk of disruption in this area is high, due to management of the IT systems and the high volume of safety signals across the network	This disruption may impact critical safety functions of the EMA and lead to delays in the identification, management and communication of product safety issues
Facilitating the development and access to medicines	There is a moderate risk of disruption in this sector. Some areas directly link to the longer-term marketing authorisation process. In other cases, the damage is on longer-term EU competitiveness	This would not result in direct impact on patients in the short-term. However, this could have a knock on effect on other parts of the regulatory process and on long-term incentives to innovate
Compliance & development of standards	This area has a lower risk of disruption as the activities require fewer EMA resources. However, some scientific and regulatory expertise, such as the coordination of inspections or the involvement in ICH are an essential support function	This would have less of an immediate effect on the public compared to the previous activities
Disseminating information	Whilst these activities are completely dependent on EMA staff, this segment is based on reports already generated through other EMA activities, and has the least potential to cause problems with business discontinuity	Many stakeholders would regard the dissemination of information very useful in driving standards and meeting regulatory requirements, but is not critical in terms of public health

High impact on public health

Medium impact on public health

Low impact on public health

Source: CRA analysis