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How to cite this publication

Please cite the final published version:

Walter, S., & Mitkidis, K. (2018). The Risk Assessment of Pharmaceuticals in the Environment: EU and US Regulatory Approach. *European Journal of Risk Regulation*, 9(3), 527-547. <https://doi.org/10.1017/err.2018.33>

Publication metadata

Title:	The Risk Assessment of Pharmaceuticals in the Environment: EU and US Regulatory Approach
Author(s):	Walter, S., & Mitkidis, K.
Journal:	<i>European Journal of Risk Regulation</i> , 9(3), 527-547
DOI/Link:	https://doi.org/10.1017/err.2018.33
Document version:	Accepted manuscript (post-print)

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THE RISK ASSESSMENT OF PHARMACEUTICALS IN THE ENVIRONMENT: EU AND US REGULATORY APPROACH

Shona Walter*, Katerina Mitkidis**

ABSTRACT

The potential exposure to organisms and humans of pharmaceutical waste presents society with a wicked problem. The health benefits of pharmaceuticals are obvious, but the public awakening to the risks posed by pharmaceutical residues in the environment is at its early stages. Regulators in the US and the EU require an environmental risk assessment of a medicinal product before it can enter the market. This article compares the US and EU approach to assessing these risks, with the purpose of providing a different perspective on how to approach this delicate balancing act of risk and benefit and to reveal the different values underpinning the risk assessment.

I. Introduction

Pharmaceuticals for human use have astounding health benefits.¹ They allow us to live longer and more productive and higher quality lives. At the same time, residue from the active pharmaceutical ingredient (API)² found in the natural environment (surface and ground water, soil and aquatic and in-land species) have been linked to negative and unintended effects on ecosystems, human health and animal health. Some pharmaceutical waste products have the ability to accumulate up the food chain and waste products from other pharmaceuticals, such as anti-cancer drugs, can directly disrupt our DNA.³ Some prominent and widely publicised examples of such negative effects include; the presence of chronic low-levels of hormones in rivers and streams that have caused sex change in fish,⁴ the decline of Indian vulture populations due to feeding off cattle treated with non-steroidal painkillers⁵ and the rise of anti-microbial resistance due to the chronic presence of antibiotics in effluent close to pharmaceutical manufacturing

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¹ This article focusses solely upon pharmaceuticals for human use, as pharmaceuticals for veterinary use undergo a different risk-benefit analysis, under a different set of regulations.

² World Health Organisation (WHO), 'WHO Technical Report Series' (2011) No. 961, Annex 10 (Procedure for prequalification of pharmaceutical products), 374-375: "active pharmaceutical ingredient (API): A substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings."

³ Jean-Philippe Besse et al., 'Anticancer drugs in surface waters: What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs?' (2012) 39 (1) Environment International, 73-86.

⁴ Susan Jobling et al., 'Widespread sexual disruption in wild fish' (1998) 32 Enviro Sci Technol, 2498; D. G. Larsson et al., 'Ethinylestradiol—an undesired fish contraceptive?' (1999) 45 Aquat Toxicol, 91.

⁵ Rhys E Green et al., 'Diclofenac poisoning as a cause of vulture population declines across the Indian subcontinent' (2004) 41(5) Journal of Applied Ecology, 793.

plants.⁶ Recently, the US Geological Survey supported a study which found that pharmaceutical residues in waste water effluent can alter fish behaviour in ways that are central to sustaining their populations.⁷

Pharmaceutical companies acknowledge the risks associated with pharmaceutical residues in the environment, but consider them insignificant compared to the benefits derived from their therapeutic use.⁸ Because of their significant value to public health, the regulatory decision to place a new pharmaceutical drug on the market requires a comprehensive assessment of all the risks and benefits of the medicine in question. During this assessment, the risks to patient health are rigorously tested and balanced against the potential therapeutic benefits of the drug. However, the environmental risks are in practice not part of this balancing act, and there is debate as to whether environmental effects should be included in the risk-benefit analysis.⁹

The PiE problem has been gaining attention of public authorities, practitioners and academics. Within the legal field, the main focus has so far been on identifying legal challenges and gaps in the general regulatory framework. In the EU context, a major contribution can be found in the BIOIS report, summarizing the legal areas needing more attention, including the marketing authorization procedures, Good Manufacturing Practices, legislation regarding chemicals, regulation of the disposal of pharmaceutical waste and water legislation. This article does not cover all the identified legal challenges, but provides a focused analysis within one of the areas. The purpose is to compare the approaches taken in the EU and the US to managing the risks posed by pharmaceuticals to the environment within the marketing authorisation (MA) in the EU and or, as it is known in the US, the new drug applications (NDAs) procedures.¹⁰ The discussion about the risks posed by pharmaceuticals in the environment is, in essence, a discussion about the

⁶ G. Joakim Larsson et al., 'Effluent from drug manufactures contains extremely high levels of pharmaceuticals' (2007) 148 Journal of Hazardous Materials, 751.

⁷ H.L. Schoenfuss et al., 'Complex mixtures, complex responses--Assessing pharmaceutical mixtures using field and laboratory approaches' (2016) 35(4) Environmental Toxicology and Chemistry, 953.
<https://toxics.usgs.gov/highlights/2015-11-13-pharmaceuticals_and_minnows.html> accessed 18 December 2017. This study is part of a larger scientific investigation investigating the health risks to humans and wildlife from low level exposure to toxic substances.

⁸ E.g. F. Hoffmann-La Roche Ltd, 'Roche Position on Pharmaceuticals in the Environment' first adopted and published 17 August 2011; reviewed in April 2017, 1 <www.roche.com/dam/jcr:05ea28bc-d654-47cb-a6ae-9d46de15b29b/en/15_Position_Pharmaceuticals-in-the-Environment_reviewed_4_2017.pdf> accessed 21 December 2017. See also European Federation of Pharmaceutical Industries and Associations (EFPIA), 'Pharmaceuticals in the Environment (PiE)' <www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/> accessed 19 December 2017.

⁹ BIO Intelligence Service, 'Study on the environmental risks of medicinal products' Final Report prepared for Executive Agency for Health and Consumers (2013), 25 (BIOIS Report). The authors of this report favour the inclusions of environmental risk assessment results into the final risk-benefit analysis. The Swedish government also supported this approach in their official response to the EU Commission's call for submission on the strategic approach to pharmaceuticals in the environment. Government Offices of Sweden, 'Swedish response on roadmap regarding strategic approach to pharmaceuticals in the environment' Memorandum 26 May 2017. The European pharmaceutical industry favours the implementation of soft law instruments rather than additional regulations and changes in policy. EFPIA et al., 'Eco-Pharmaco-Stewardship (EPS) A Holistic Environmental Risk Management Program', 5 <www.efpia.eu/media/25628/eps-a-holistic-environmental-risk-management-program.pdf> accessed 21 December 2017.

¹⁰ When referring to these EU and US procedures together, the term 'regulatory procedures' is used. The term 'medicine' is used to cover both the US legal term 'drug' and the EU legal term 'medicinal product'. The term E(R)A is used to refer to the both the EU 'Environmental Risk Assessment' procedure and the US 'Environmental Assessment' procedure.

love/hate relationship society has with hazardous substances.¹¹ Some critics argue that medicines are given more leeway or regulated in a more relaxed manner than other hazardous substances, due to the significant health benefits they provide.¹² A debate about the risks and benefits of pharmaceuticals will always be controversial, as risks tend to lie with the more vulnerable sectors of society and the benefits with the more informed and powerful sectors of society.¹³ It also requires a balancing act of different values, namely public health versus the environment and the priority placed upon these values can differ from place to place.¹⁴

This article undertakes a comparative analysis of the EU and US pharmaceutical regulatory procedures in the context of the pharmaceuticals-in-the-environment problem (PiE), in order to detect the differences and similarities and to ask ourselves if there is a better way forward.¹⁵ The reason to focus this research on EU and US law is because these two regions are responsible for about two thirds of the global consumption of pharmaceutical drugs.¹⁶ Pharmaceutical residue predominantly enters the environment via patient use.¹⁷ There is also a rich academic debate discussing the differences and similarities of the US and EU approach to risk assessment of products in general. Some of this debate has taken place under the guise of some well-known trade disputes, for example the WTO Hormones decision.¹⁸ Another reason is that the EU and the US are both founding members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The purpose of this organisation is to achieve greater global harmonisation of laws concerning human medicines. The European Commission and the US Food and Drug Authority (FDA) have committed to implementing the guidelines produced by the ICH.¹⁹ Therefore, comparing the differences and similarities of the US and EU will provide an insight into the progress made into harmonising the law in this area.

Part II. of the article begins by outlining the main known and unknown risks pharmaceuticals pose to the environment. It also explains the main gaps in our scientific knowledge about the environmental effects of pharmaceuticals. Part III. of the paper gives a critical analysis of the US and EU's approach to assessing the risks posed by pharmaceuticals to the environment. There are many different ways to approach risk management and to address all aspects of the law in this area is beyond the scope of the paper. Therefore, this article focuses on the pharmaceutical regulatory procedures, and directly compares EU and US

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¹¹ E.g. Rachel Carson, *Silent Spring* (Houghton Mifflin 1962); Soren Lokke, 'The Precautionary Principle and Chemicals Regulation' (2006) 5 Environment Science Pollution Resources, 342; David Taylor et al., 'Human pharmaceutical products in the environment – The "problem" in perspective' (2014) 115 Chemosphere, 95.

¹² Taylor et al., *supra*, note 11.

¹³ Garric E. Louis et al., 'Representing inequities in the distribution of socio-economic benefits and environmental risk' (2002) 79 Environmental Monitoring and Assessment, 102.

¹⁴ David Taylor, 'There is a Conflict at the Heart of EU Water Pollution Policy' (2015) 3 EJRR, 430.

¹⁵ This article examines the EU level of regulation within the EU context and the federal level of regulation within the US context. Differences at national and state level respectively are not addressed.

¹⁶ In 2016, the global sale of pharmaceutical drugs was estimated at USD\$ 967 billion. The US was responsible for USD\$ 446 billion and the EU for USD\$ 201 billion <www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/> accessed 10 October 2017.

¹⁷ Hans Sanderson et al., 'Ranking and prioritization of environmental risks of pharmaceuticals in surface water' (2004) 39 Regulatory Toxicology and Pharmacology, 159. 10-70% of orally administered medicines' active ingredients are metabolised by the body, the rest are excreted and end up in the wastewater treatment system, BIOIS Report, *supra*, note 9, 19.

¹⁸ 'US - EC Measures Concerning Meat and Meat Products (Hormones)' WT/DS26/R/USA, 18 August 1997; Report of the Appellate Body, 'EC Measures Concerning Meat and Meat Products (Hormones)' WT/DS48/AB/R, 16 January 1998. This decision is discussed in Part II, section 3 below.

¹⁹ <www.ich.org/about/mission.html> accessed 18 October 2017.

provisions which deal with the assessment of the environmental effects under this procedure, also known as the environmental risk assessment (ERA) in the EU and environmental assessment (EA) in the US assessment stage.²⁰ It then compares the legal requirements to assessing the risk to the environment. The article concludes with a discussion of the findings and provides a different perspective on how to manage the risk of PiE. This is highly topical as the European Commission is currently preparing a strategic approach to PiE.²¹

II. What do we (not) know

As briefly outlined in the Introduction, the environmental risk is just one of the weights on the scale when balancing the risks and benefits of a new drug entering the market and a weight that has so far been treated as a marginal one, as demonstrated in the following discussion.

In terms of their direct impact on human beings through their safety, quality and efficacy characteristics, pharmaceuticals are strictly evaluated before placed on the market.²² However, when it comes to assessing their impact on the environment - including their indirect impact on human health -, there are obvious gaps in the applicable EU and US law, which arguably need addressing. Before the law can strike an appropriate balance between protecting patient's access to good quality medicines and protecting the environment, gaps in our scientific knowledge must be addressed.²³ These gaps are caused by both regulatory practices and scientific limitations.

Firstly, the questions about the effects of pharmaceutical residues on the natural environment are often treated separately from the questions of the effects of pharmaceutical residue on human health. The World Health Organisation (WHO) concluded that pharmaceuticals in drinking water do not pose a threat to human health.²⁴ Pharmaceutical companies second this position. For example, Roche contends that the levels at which pharmaceuticals have been found in the environment are in general too low to have an adverse effect on humans,²⁵ and thus too low to trigger a detailed environmental risk assessment.²⁶ Nevertheless, some scientific studies have established that the levels of pharmaceuticals found in discharge from waste-water treatment plants are high enough to be harmful to aquatic species²⁷ and through this also harmful to humans. Therefore, the simplistic view of seeing human health as separate from environmental health is not correct when you consider the effects upon humans from exposure to

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²⁰ Supra, note 10.

²¹ European Commission, 'Strategic approach to pharmaceuticals in the environment, DG ENV, Ares(2017)2210630, 28 April 2017.

²² In the EU context, Directive 2001/83/EC. In the US context, the United States Code, Title 21 Food and Drugs, Chapter 9 Federal Food, Drug and Cosmetic Act, subchapter 5, section 355(1)(a) (21 U.S.C. §355(1)(a)).

²³ The European Union has financed several research projects focused on improving the ERA of pharmaceuticals, see e.g. Environmental Risk Assessment of Pharmaceuticals (ERA Pharm), the aim of the project was to advance existing knowledge and methods for evaluating potential risks posed by human and veterinary medicines to the environment, <www.erapharm.org/> accessed 20 December 2017. EMCO, a project which aimed to reduce environmental risk, posed by emerging contaminants, through advanced treatment of municipal and industrial wastes, <http://cordis.europa.eu/project/rcn/74202_en.html> accessed 20 December 2017.

²⁴ WHO, 'Pharmaceuticals in Drinking-water' (2011) WHO/HSE/WSH/11.05, 28 ("Analysis of the results indicated that appreciable adverse health impacts to humans are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in drinking-water.")

²⁵ F. Hoffmann-La Roche Ltd, supra note 8, 1.

²⁶ European Medicines Agency, 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use', EMEA/CHMP/SWP/4447/00 corr 2 (2006), 3 (EMA Guidelines).

²⁷ Evelyn Touraud, 'KNAPPE Report' (2008), 1 <http://environmentalhealthcollaborative.org/images/KNAPPE_REPORT_FINAL.pdf> accessed 21 December 2017.

pharmaceutical residues in water and soils.²⁸ In fact, the effects of long-term chronic exposure to even low levels of pharmaceuticals is one of the main topics in both academic and practitioners' discourse.²⁹

The second major issue is a lack of scientific data. Public authorities in the US and EU in general do not routinely test for the presence of pharmaceuticals in water and soils.³⁰ The WHO recognises this lack of good scientific data makes it challenging to effectively assessing the human health risks from exposure to pharmaceutical residues.³¹ In addition, confidential data generated during the MA process in the EU and US is private, making it very challenging for individuals and NGOs to inform themselves about the environmental risks posed by pharmaceuticals.³² This in turn presents a significant barrier for informed decision making in the public sphere about the risks and benefits of pharmaceuticals.

Lastly, the current approach to assessing the risks of medicines in the EU and US is for a particular medical product, not for the API within the medicine.³³ This approach is not effective in assessing the cumulative impact of PiE. Once pharmaceuticals enter the waste water system, they are mixed with other pharmaceuticals and all the other kinds of chemicals we use on a daily basis, and there is very little knowledge about the long-term effect these mixtures could have.³⁴ The WHO has also acknowledged there is not enough knowledge about the effects of long-term chronic exposure to pharmaceuticals and the possible combined effects of mixtures upon organisms in water and soil.³⁵

The known impacts of pharmaceuticals on the environment together with much less documented impacts of pharmaceuticals residue on human health call for precaution.³⁶ While we cannot speak about scientific certainty regarding the detrimental effects on human health, there is a growing scientific evidence of the same.³⁷ This calls for more attention to the environmental risks during pharmaceutical regulatory procedures.

III. Analysis

²⁸ For example, antimicrobial resistance (AMR) has been directly related to the chronic presence of low levels of antibiotics in the environment. Klaus Kummerer, 'Antibiotics in the aquatic environment—a review—part II' (2009) 75(4) Chemosphere, 417. In the US, every year at least 2 million people are infected by bacteria resistant to antibiotics, which leads to 23,000 deaths because of these infections <www.cdc.gov/drugresistance/index.html> accessed 9 November 2017.

²⁹ Concerning the effects upon aquatic species from long-term chronic exposure to endocrine disrupting substances see Susan Jobling et al., 'Ethinyl oestradiol in the aquatic environment' ch 13 in European Environment Agency, *Late lessons from early warnings*, EEA Report No.1/2013; concerning the effects of AMR see Kummerer, supra, note 282831.

³⁰ In the US, Pharmaceuticals and Personal Care Products are not regulated in surface and drinking water, meaning that we have no reliable data about the level of their presence. National Environmental Services Center at West Virginia University, *Pipeline* (Winter 2007) 18(1), 1.

³¹ WHO, supra, note 242427, 6.

³² For more detailed discussion on the same, see Part III, section 3 below.

³³ By comparison, Regulation (EC) 1907/2006 of the European Parliament and of the Council of 18th December 2006 concerning the Registration, Authorisation and Restriction of Chemicals [2006] OJ L 396 1 (REACH Regulation) considers multiple sources of exposure from a substance or similar substances.

³⁴ SCHER, SCCS, SCENIHR, 'Opinion on the Toxicity and Assessment of Chemical Mixtures', European Union (2012), 30.

³⁵ WHO, supra, note 242427, 29. See also Touraud, supra, note 272730, 1. Some possible effects include endocrine disruption, disruption of microbial ecosystems, growth inhibition, cytotoxicity, mutagenicity and teratogenicity; E. Silva et al., 'Something from "nothing" — Eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects', (2002) 36/8 (1) Environ. Sci. Technol., (36/8), 751.

³⁶ This article does not discuss the possible use of the precautionary principle for managing the risks of PiE.

³⁷ Jobling et al., supra, note 292932, 279.

This part describes and compares the current use and practice of E(R)A in the EU and the US pharmaceutical registration procedures. It starts by exploring the relevance and weight of the E(R)A within these procedures. Then moves onto the scope of the ERA, and lastly compares the requirements related to assessment panels and public access to information. Reflections on the comparison are summarised in the Conclusion.

1. Relevance and weight of the E(R)A

The main focus of this article is to compare how the EU and US balance the risks to the environment against the benefits of using pharmaceutical drugs. A crucial part of this analysis is the impact the E(R)A has upon the risk-benefit analysis within the regulatory procedures. At a glance, the US and EU take a very similar position. Under both jurisdictions, the drug may be approved, even if the E(R)A shows there will be an adverse impact on the environment. However, there are slight differences in their approach when you take a closer look.

Directive 2001/83/EC contains the European Union code for medicinal products of human use, covering issues from marketing authorization procedure to the disposal of unused pharmaceuticals. Article 8 sets out what must be included in the application for a MA of a new medicinal product. Article 8(3)(ca) states that an evaluation of the potential environmental harm, so-called environmental risk assessment (ERA), must be included in the application.³⁸ Article 8(3)(ca) is a relatively new requirement and came into force in October 2005.³⁹ This amendment can be seen as an expression of the integration principle as required by Article 11 of the Treaty of the Functioning of the European Union (TFEU).⁴⁰ Annex I, section 1.6 contains further details which the applicant must provide in the ERA, details of this will be discussed later on in the article.

The United States takes a slightly different approach to regulating the effects of pharmaceuticals in the environment. The law in this area is contained in several pieces of legislation. The passing of the National Environmental Policy Act (NEPA) in 1969 under President Nixon, brought in the era of America's modern environmental laws.⁴¹ NEPA 'requires all Federal agencies to assess the environmental impact of their actions', and the FDA must implement this requirement by assessing the environmental impact of drugs during the new drug application (NDA) process.⁴² Title 21, Part 355(a) of the United States Code (U.S.C.),⁴³

³⁸ Directive 2001/83/EC, art 8(3)(ca) "Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged."

³⁹ However, art 8(3)(ca) of Directive 2001/83/EC was not the first implementation of environmental concerns into the European Pharmaceutical law. The first such inclusion of environmental protection can be found in art 4(6) of Council Directive 65/65/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products [1965] OJL 22, 369, introduced in 1994 ("If applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment.") See also Per Spindler et al., 'Environmental Assessment for Human Medicines in the European Union' (2007) 41 Drug Information Journal, 149.

⁴⁰ Consolidated Version of the Treaty on the Functioning of the European Union (2016) OJ C 202, Art. 11, 'Environmental protection requirements must be integrated into the definition and implementation of the Union policies and activities, in particular with a view to promoting sustainable development.'

⁴¹ 42 U.S.C. §4321 et seq. (1969).

⁴² U.S. Department of Health and Human Services, et. al., 'Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications', July 1998 ('U.S. Guidance for industry'), 1.

⁴³ The United States Code, also known as the Code of the Laws of the United States of America, is the codification and compilation of the federal statutes of the United States. They are the Acts of Congress, which are then signed by the President.

creates the necessity to apply for the approval of any new medicine that wishes to enter interstate commerce.⁴⁴ Part 355(b)(1)(A) requires the applicant to include full reports of investigations showing 'whether or not the drug is safe for use and whether such drug is effective in use.' In addition to this, NEPA requires the FDA to assess the environmental impact of new medicines which seek the FDA's approval to market a new medicine (Marketing Approval - MA).⁴⁵ Title 21, part 25.15 and 25.20 of the Code of Federal Regulations (CFR) sets out the requirement to submit an environmental assessment (EA) when an applicant applies for the MA of a new medicine.⁴⁶ The FDA also has the power to refuse to file or approve an application for a new medicine if the applicant fails to provide an adequate E(R)A, or a claim of categorical exclusion.⁴⁷ An adequate E(R)A is one which addresses 'the relevant environmental issues', and needs to provide the FDA with enough information to decide whether the new medicine could 'significantly affect the quality of the human environment.'⁴⁸

EU law takes a lenient approach to the obligation to submit a satisfactory E(R)A during the MA procedure. Practice indicates that an incomplete or missing E(R)A will not prevent a MA being given for a new medicine.⁴⁹ A study in 2014 found that 37% of the E(R)As for products registered through the centralized procedure carried out between 2011 – 2012, were submitted after the deadline.⁵⁰ They also found that 83% of the E(R)As submitted were of an incomplete or unsatisfactory nature.⁵¹ This same study noted this lack of compliance with the time-frame to submit an E(R)A indicates companies do not prioritise E(R)A-related issues during the MA procedure.⁵² A major reason for a MA being given to a medicine despite a missing E(R)A is because the E(R)A is not part of the risk-benefit analysis.⁵³

Article 2 of the 2001 Directive clearly states the following:

'28. Risks related to use of the medicinal product:

- any risk relating to the quality, safety or efficacy of the medicinal product as regards patient's health or public health;*
- any risk of undesirable effects on the environment.*

28a. Risk-benefit balance:

*An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, **first indent**.*' (emphasis added)

Because environmental risks are not included in the risk-benefit analysis, the E(R)A results have no impact on the final approval of a medicine. When there is an undeniable impact on the environment, risk management measures 'shall be envisioned'.⁵⁴ The pharmaceutical industry supports the approach of

⁴⁴ 21 U.S.C. § 355.

⁴⁵ 21 CFR 25.15; 21 CFR 25.20(l). The Code of Federal Regulations is a codification of the rules and regulations published by the federal government and executive departments and agencies of the United States.

⁴⁶ 21 CFR 25.15; 21 CFR 25.20.

⁴⁷ 21 CFR 314.101(d)(4), 601.2(a) and (c), and 25.15(a)). The categorical exclusions will be discussed later on in the paper.

⁴⁸ 21 CFR 25.15(a).

⁴⁹ BIOIS Report, *supra*, note 9, 146.

⁵⁰ Laura Caneva et al., 'Critical review on the environmental risk assessment of medicinal products for human use in the centralised procedure' (2014) 68 Regulatory Toxicology Pharmacology, 312.

⁵¹ *Ibid.*, 313.

⁵² *Ibid.*, 315.

⁵³ BIOIS Report, *supra*, note 9, 130. See also Caneva, *supra*, note ~~505053~~, 315.

⁵⁴ Directive 2001/83/EC, Art. 8(3)(ca).

granting MAs with post-marketing commitments, such as the submission of an E(R)A and monitoring under the pharmacovigilance system,⁵⁵ or eco-pharmacovigilance,⁵⁶ when considering environmental endpoints.⁵⁷ Those who defend the exclusion of the E(R)A from the risk-benefit analysis argue lawmakers tried to reflect societies concern that if environmental impacts were relevant in the ultimate balancing act of risks and benefits, then a potentially lifesaving medicine could be refused on the basis of its environmental impact.⁵⁸ Those who argue for the consideration of the E(R)A results during the risk-benefit analysis, state that its inclusion would be very unlikely to result in the exclusion of new medicines on the market. Rather it should target the approval of known problematic APIs.⁵⁹ This would be done by balancing the expected therapeutic benefits against the environmental impact, with particular consideration of whether there are already alternative and equivalent treatments available with less environmental impact.⁶⁰

Risk assessment involves the balancing of different values and the European Court of Justice in the *Pfizer* decision discussed (amongst other things) how the EU institutions determine the acceptable level of risk and thereby the level of protection given to each value.⁶¹ The court explains this is done by the EU institutions defining the political objectives to be pursued through a certain legal measure, within the bounds of the powers given to them by the Treaties.⁶² The legal basis of Directive 2001/83/EC is the internal market.⁶³ Article 114 of the TFEU governs the EU's law making power in furtherance of the internal market. Article 114(3) states that the Commission must assign a high level of protection to health and the environment when making their proposal. This 'high level of protection' is reflected in the second paragraph of the preamble,⁶⁴ making the Directive's objective a set of rules allowing for the free movement of high quality and safe medicinal products. The environment arguably has less value under EU pharmaceutical law when it concerns human medicines. This could be because the possible detrimental effects on aquatic and land species is considered less significant than the availability of medicines and the competitiveness of the European pharmaceutical industry on the global market.⁶⁵ However, as argued above, this is a simplistic view ignoring any indirect effects of pharmaceutical residue in the environment on human health.

The US District Court for the Southern District of New York, in the case *Natural Defence Council v. United States Federal Drug Authority*, also discussed the threat of AMR due to non-therapeutic use of antibiotics in

⁵⁵ Directive 2001/83/EC, Art. 1(28d).

⁵⁶ AESGP, EFPIA & EGA, *supra*, note 9.

⁵⁷ Touraud, *supra*, note 272730, 4.

⁵⁸ Melanie Gross et. al., 'Environmental Risk Assessment of Human Pharmaceuticals: Regulatory Developments' (2016) 12(1) *Journal of Integrated Environmental Assessment and Management*, 7-8 (retracted).

⁵⁹ Marlene Agerstrand et al., 'Improving Environmental Risk Assessment of Human Pharmaceuticals' (2015) 49 *Environmental Science and Technology*, 5341.

⁶⁰ *Ibid.*

⁶¹ Case T-13/99 *Pfizer Animal Health SA v Council of the European Union* [2002] ECR II-3305. The *Pfizer* decision concerned the risks of AMR due to the non therapeutic use of antibiotics in the feed of animals for human consumption and is widely known for its discussion of the precautionary principle.

⁶² Case T-13/99 *Pfizer Animal Health SA v Council of the European Union* [2002] ECR II-3305, paragraph 150-151.

⁶³ The Directive refers to Article 95 of the Treaty establishing the European Community, now Article 114 of the Treaty on the Functioning of the European Union (TFEU).

⁶⁴ Directive 2001/83/EC, Preamble, paragraph 2 'The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.'

⁶⁵ Commission, 'Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector', COM 666 final, 3. "Since 1965, Community action in the field has always had the dual objective of safeguarding public health by providing Europe with safe and effective medicines, while at the same time creating a business environment that stimulates research, boosts valuable innovation and supports the competitiveness of the industry."

animals for human consumption.⁶⁶ The court ruled that when the FDA decides to approve a NDA or withdraw an existing medicine from the market, 'the inquiry focusses on whether the drug is safe and effective.'⁶⁷ This includes the requirement to submit 'full reports of investigations which have been made to show whether or not such drug is safe and effective for use.'⁶⁸ In essence, the FDA was found to have not evaluated the science presented by the plaintiff describing the risk of AMR, nor did they assess the safety of the relevant drugs.⁶⁹ The court confirmed the statutory mandate for the FDA's action comes from Congress⁷⁰, and upheld the decision of *Massachusetts v. EPA*, that an agency "must ground its reason for action or inaction in the statute."⁷¹

In the US, when preparing an E(R)A, the applicant is required to consider if there were other possible solutions available which were less environmentally damaging, and if this course of action was not taken, they must explain why it was not taken.⁷² This balancing act is a practical example of how to include the E(R)A results into the risk-benefit analysis and should be picked up by critics of EU law, who seek for the inclusion of the E(R)A results in a similar fashion. If the FDA decides to approve a new medicine, they can require the applicant to implement any measures mitigating the drug's effect on the environment and make these mitigating measures part of the drugs approval.⁷³ The FDA can also withdraw approval of the drug if new information becomes available showing a serious adverse effect upon the environment.⁷⁴ This is similar to the pharmacovigilance system under EU law, which will also review the MA if new information becomes available relating to the safety of the drug.⁷⁵

Under EU law, Annex I section 1.6 of the Directive 2001/83/EC contains a more detailed requirement of the ERA and is directed solely at the applicant. The applicant 'shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product'.⁷⁶ This is in contrast to the US approach, where first the applicant is required to provide an EA.⁷⁷ The FDA will then evaluate the EA to ensure it is objective and accurate, and determine if the drug's approval will 'significantly affect the quality of the human environment'.⁷⁸ If the FDA finds this to be the case, they will produce an environmental impact statement (EIS).⁷⁹ These two features of the law, the legal requirement to ensure that the EA is objective and accurate and the possibility of the FDA producing their own assessment of the potential environmental impacts, leads to the conclusion that the US approach arguably has more checks in place to ensure the environmental assessment is of a high standard. However, this

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⁶⁶ *Natural Defence Council, INC., et al. v. United States Food and Drug Administration, et al.*, U.S. Dist. Court Southern District N.Y. 42 ELR 20117. Decided 1 June 2012.

⁶⁷ *Ibid.*, 15.

⁶⁸ *Ibid.* See also 21U.S.C. § 360b (b)(1)(A).

⁶⁹ *Ibid.*

⁷⁰ *Ibid.*, 18.

⁷¹ *Massachusetts v. EPA*, 549 U.S., 535. *Natural Defence Council, INC., et al. v. United States Food and Drug Administration, et al.*, 42 ELR 20117, 16.

⁷² CFR Part 25.40(a)

⁷³ CFR Part 25.40(e).

⁷⁴ CFR 25.52(b).

⁷⁵ Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [2010] OJ L 348.

⁷⁶ Directive 2001/83/EC, Annex 1, sec 1.6.

⁷⁷ CFR title 21, part 25.15 (a).

⁷⁸ CFR title 21, part 25.15 (b).

⁷⁹ CFR title 21, part 25.15 (b).

might not be the case as the application of the US law is largely limited by the categorical exclusions, as will be shown below.

2. Scope of the Environmental Risk Assessment

This section highlights the main differences and similarities of what the law in the EU and US includes under the scope of the E(R)A.

As both the EU and US, along with Japan, are founding members of the ICH, they must adopt the guidelines issued by this body. To date the ICH has issued guidelines for the testing of the following effects of medicines during the market authorisation procedure: carcinogenicity,⁸⁰ genotoxicity,⁸¹ chronic toxicity,⁸² reproductive toxicity,⁸³ and immunotoxicity.⁸⁴ There are no guidelines which address the risk of medicinal residues in the environment, which could be one explanation for the lack of harmonisation between the EU and US in this area.

A common feature of the scope of the E(R)A under EU and US law is if the medicine is unlikely to significantly affect the environment, the applicant is not required to prepare an E(R)A.⁸⁵ Under US law, the FDA will consider the cumulative effect of the medicine upon the environment.⁸⁶ This is not the case under EU law, where the potential environmental concentration (PEC) of the medicine is calculated on an individual basis.⁸⁷ Interestingly under EU law if the medicine has endocrine disrupting properties, the applicant will still be required to perform an E(R)A even if the medicine does not present a risk. Conversely, US law does not consider the risk posed by endocrine disrupters to aquatic species, even at very low levels.⁸⁸

A striking difference between the US and EU is the approach to considering the effects upon the environment from manufacturing effluent. In the US, the applicant must consider the risks from manufacturing effluent to endangered species and habitats critical for those species. Under section 25.21(b) of the CFR, the FDA will require an E(R)A if a species or critical habitat protected under federal law or under the Convention on the International Trade in Endangered Species of Wild Flora and Fauna (CITES)⁸⁹ could be adversely affected by the approval of a NDA.⁹⁰ Guidelines issued by various federal

⁸⁰ ICH, 'Testing for Carcinogenicity of Pharmaceuticals S1B' dated 16 July 1997.

⁸¹ ICH, 'Guidance on Genotoxicity testing and Data Interpretation for Pharmaceuticals intended for Human use S2(R1)' dated 9 November 2011.

⁸² ICH, 'Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) S4' dated 2 September 1998.

⁸³ ICH, 'Detection of Toxicity to Reproduction for Medical Products & Toxicity to Male Fertility S5(R2)' dated 24 June 1993.

⁸⁴ ICH 'Immunotoxicity Studies for Human Pharmaceuticals' dated 15 September 2005.

⁸⁵ Under US law CFR title 21, part 25.15(c) uses the term 'not significantly affecting the human environment'. Under EU law, the EMA Guidelines state that if the predicted environmental concentration (PEC) of the medicine is below a certain level, it is not considered a risk to the environment. EMA Guidelines, 5.

⁸⁶ CFR title 21, part 25.15(c).

⁸⁷ EMA Guidelines, *supra*, note [262629](#), 4. Any medicine which has a PEC below a certain value is not considered a risk.

⁸⁸ See CFR title 21, part 25.15 General Procedures.

⁸⁹ CFR title 21, part 25.21(b) specifically mentions the Endangered Species Act of 1973, the Convention on the International Trade in Endangered Species of Wild Flora and Fauna (signed at Washington, D.C., on 3 March 1973, entered into force 1 July 1975) and any endangered wild flora or fauna entitled to protection under federal law.

⁹⁰ CFR title 21, part 25.21(b).

bodies, including the FDA, require applicants to consider the adverse effects from manufacturing emissions upon species or habitats protected under the abovementioned laws.⁹¹ By considering species protected under CITES and the Endangered Species Act, section 25.21(b) requires applicants to consider the effects of manufacturing effluent upon species outside of the US.⁹² This is significant because China and India account for up to 90% of the global production of antibiotics.⁹³ An investigation revealed that poor manufacturing practices in China led to the release of antibiotics into the local environment, making these factories an important contributor to the global problem of antimicrobial resistance.⁹⁴

Unlike US law, applicants under the EU MA procedure are not required to consider the effects upon the environment from the manufacture of medicines.⁹⁵ Presumably, the Industrial Emissions Directive (IED) would cover the release of pharmaceuticals from manufacturing processes.⁹⁶ Annex II of the IED lists the substances for which monitoring and emission limit values should be set. To date, Annex II does not list any active pharmaceutical ingredient (API). Consequently, pharmaceutical manufacturers are not required to specifically control the emission of APIs into the air or water.⁹⁷ In addition unlike the US, applicants under the MA procedure in the EU are not required to evaluate the impact of the medicine upon endangered or protected species in the EU.⁹⁸ Nor does it mention the need to consider the impact upon sites within the Natura 2000 network.⁹⁹ By comparing the scope of the E(R)A in this instance, it surprisingly appears that the US places more value on the protection of endangered species and their habitats than the EU.

Another commonality between the EU and US is that there are a large number of exceptions to the requirement to submit an E(R)A during the MA procedure. Part 25.31 of the CFR lists the numerable exemptions which relate to human drugs.¹⁰⁰ In general, if the proposed approval of the drug does not result

⁹¹ CFR title 21, part 25.40(c) encourages applicants to consult 'FDA EA guidance documents, which provide additional advice on how to comply with FDA regulations.' CFR title 21, part 25.21. See also U.S. Guidance for Industry, supra, note 424245, pp. 6-7.

⁹² CITES covers species located all over the world <<http://checklist.cites.org/#/en>> accessed 24 November 2017. The Endangered Species Act of 1973 protects 631 species located outside of the US, see <<https://ecos.fws.gov/ecp0/reports/ad-hocspeciesreport?status=E&status=T&status=EmE&status=EmT&lead=10&header=Foreign+Species&fleadreg=on&fstatus=on&finvpop=on>> last accessed 24 November 2017.

⁹³ SumOfUS, 'Bad Medicine –How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs' June 2015 <www.sumofus.org> accessed 21 December 2017, 7.

⁹⁴ Ibid., 26. This report recommends that legislators in the EU and US should revise the Good Manufacturing Practices (GMP) to include environmental criteria, such as water quality standards and good waste management (see p. 35). Companies wishing to import antibiotics to the US and EU are required to comply with the GMP guidelines, see Directive 2001/83/EC Art. 46b(1) and 21 U.S.C. §381(a) & §360j(f).

⁹⁵ The EMA Guidelines explicitly state that "Directive 2001/83/EC, as amended, relates to those risks to the environment arising from the use, storage and disposal of medicinal products and not to risks arising from the synthesis or manufacture of medicinal products." EMA Guidelines, supra, note 262629, 3.

⁹⁶ Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (formally known as the integrated pollution prevention and control) [2010] OJ L 334.

⁹⁷ National legislation from Sweden, Germany and the Netherlands also do not include emission limit values for APIs, see BIOIS report, supra, note 9, 152.

⁹⁸ For example, any species listed in Annex II of the Habitats Directive or Annex I of the Birds Directive. Directive 92/43/EEC on the Conservation of Natural Habitats and of Wild Fauna and Flora ('Habitats Directive') [1992] OJ L206/7, Directive 79/409/EEC on the Conservation of Wild Birds ('Birds Directive') [1979] OJ L103/1.

⁹⁹ Habitats Directive Art. 3. See also European Commission, Natura 2000, <ec.europa.eu/environment/nature/natura2000/index_en.htm> accessed 19 December 2017.

¹⁰⁰ CFR title 21 part 25.31.
Human drugs and biologics.

in an increase in the use of the relevant active ingredient (25.31(a)) and/or an increase of discharge into the environment (25.31(b)), it will be covered by the categorical exclusion. In 1997, the number of categorical exemptions were significantly increased, due to President Clinton's reinventing government (REGO) initiatives.¹⁰¹ According to critics of this reform, a result of these REGO initiatives were that only drugs whose sales exceeded 44 tonnes per year required an E(R)A.¹⁰²

Despite this cutting of green tape, the FDA still has the right to require an E(R)A in extraordinary circumstances. Under part 25.21 of the CFR, even if the applicant is entitled to a categorical exclusion, the FDA will still require an E(R)A in extraordinary circumstances. Namely if the 'action may significantly affect the quality of the human environment'.¹⁰³ There are two specific examples of an extraordinary circumstance given in the CFR.¹⁰⁴ Firstly, situations where the data points to 'the potential for serious harm to the environment'; this includes long-term effects on the functioning of ecosystems and toxic effects on organisms.¹⁰⁵ Secondly, direct and indirect effects (e.g. effluent from manufacturing), which could adversely affect an endangered species or habitat critical for that species survival.¹⁰⁶

Similar to the US, under the EU MA procedure not all applicants are required to provide an E(R)A. Since 30 October 2005, all applicants seeking a MA for both original and generic pharmaceutical products,¹⁰⁷ must submit an ERA with their applications. There are however some exceptions that apply to medicines authorised prior to 30 October 2005. For applications that present a 'major variation'¹⁰⁸ of a previously authorised medicine, the applicant must submit an ERA only if there is an expected increase in environmental exposure.¹⁰⁹ Similarly, applications to extend a MA are only required to include an ERA if

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The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) ...if the action does not increase the use of the active moiety.

(b) ...the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

(c) ...for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

¹⁰¹ U.S. Guidance for Industry, supra, note [424245](#), 1.

¹⁰² Gross, supra, note [585861](#), 6.

¹⁰³ 21 CFR part 25.21(b) *Extraordinary circumstances*.

As required under 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (see 40 CFR 1508.27 for examples of significant impacts). Examples of such extraordinary circumstances include:

(a) ...the potential for serious harm to the environment; and

(b) Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law.

¹⁰⁴ However, these two examples do not limit the meaning of the term 'extraordinary circumstance'.

¹⁰⁵ CFR part 25.21 (a). U.S. Guidance for Industry, pp. 6-7.

¹⁰⁶ CFR part 25.21 (b). This includes species or habitat protected under the Endangered Species Act, or the Convention on International Trade in Endangered Species of Wild Fauna and Flora, or protected under some other Federal Law; see U.S. Guidance for Industry, supra, note [424245](#), 6-7.

¹⁰⁷ Directive 2001/83/EC Art. 10(2)(b) 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product.

¹⁰⁸ Also known as Type II variations, this is a change which may have an effect on the safety, efficacy or quality of the medicine concerned.

¹⁰⁹ EMA Guidelines, supra, note [262629](#), 3. In this situation, the MA holder can reuse environmental information submitted in the original application.

there is a potential increase of environmental exposure.¹¹⁰ The authors of the BIOIS report argue that in practice this means that medicines authorised prior to 30 October 2005 are not required to carry out an ERA.¹¹¹ This is significant because the number of new active pharmaceutical ingredients arriving onto the market is likely to be small, compared to what has been authorised in the past. Some of these older generic medicines are the main culprits in the contamination of surface water in the EU.¹¹² Moreover, according to the EU EMA Guidelines, some pharmaceuticals instead of submitting an E(R)A, can provide a justification showing why there is no significant risk to the environment.¹¹³

Experts from the BIOIS Report furthermore argue that the requirement to submit an E(R)A has no retroactive effect.¹¹⁴ This is significant from an environmental perspective because the ten most commonly found pharmaceuticals in drinking water were given a MA before 2004, therefore they were not required to submit an E(R)A during their MA application.¹¹⁵ However, in 2004 the 2001 Directive was amended by inserting the condition that the MA is valid for only five years.¹¹⁶ After this period a MA may be renewed after an evaluation of a risk-benefit analysis.¹¹⁷ It could thus be reasonably expected that potential environmental risks of the 'old' medicinal product should be assessed when an MA is renewed.

Another point of difference from the US law is when preparing the E(R)A, applicants under EU law whose product contains Genetically Modified Organisms (GMOs), must comply with a special set of requirements set out in Annex I, section 1.6 of the Directive 2001/18/EC.¹¹⁸ This includes preparing a risk management strategy, designed to address the risk of GMOs to the environment. This is strikingly different from US law, which makes no specific mention of the need to address risks associated with GMOs. When you can pinpoint a real difference in how countries manage the same risk, Jasanoff argues this is a sign that different countries have different values and politicians within those countries have made certain commitments to their electorate to uphold their values.¹¹⁹ It is well known that the EU is more adverse to GMOs than the US.¹²⁰ Hornsby argues the European's scepticism of GMOs stems from well-publicised food scares.¹²¹ Consequently, very few Europeans are willing to trust their governments when it comes to biotechnology, hence the negative public perception of GMOs and the science behind it.¹²² In addition, the

¹¹⁰ European Medicines Agency, 'Questions and answers on 'Guidelines on the environmental risk assessment of medicinal products for human use' EMA/CHMP/44609/2-10, 4.

¹¹¹ BIOIS Report, supra, note 9, 117.

¹¹² Ibid., 118.

¹¹³ See <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500205987.pdf> accessed 21 December 2017. The interpretation of the guidelines has not been clear on this point and the EMA is due to issue a revised set of Guidelines clarifying this issue and others in 2018.

¹¹⁴ BIOIS Report, supra, note 9, 117.

¹¹⁵ Ibid., 118.

¹¹⁶ Directive 2001/83/EC Art. 24(1) 'Without prejudice to paras. 4 and 5, a marketing authorisation shall be valid for five years.'

¹¹⁷ Directive 2001/83/EC Art. 24(2) 'The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.'

¹¹⁸ Directive 2001/83/EC Annex I, 1.6. Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms [2001] OJ L106/1.

¹¹⁹ Jasanoff, supra, note ~~Fejll Bogmærke er ikke defineret.Fejll Bogmærke er ikke defineret-16~~, 369.

¹²⁰ On 1st October 2001 the US, supported by Canada launched two official protests before the SPS Committee, in protest to the requirements contained in the Directive 2001/18/EC. In particular, they disagreed with the requirement to the labelling and traceability of GM produce and the approval process. David J. Hornsby, *Risk Regulation, Science, and Interests in Transatlantic Trade Conflicts*, Palgrave Macmillan 2014, 142 & 158.

¹²¹ For example, mad cows disease, dioxin contamination and hormone fed beef. Ibid., 143.

¹²² Ibid., 143.

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US biotech and agricultural industry has been very influential in shaping public opinion and GMO regulations, and more organised than their European counterparts.¹²³

In both the EU and US, the applicant is required to develop risk mitigation measures if there is an unavoidable risk to the environment. In the US, the FDA can impose the obligation to implement the risk mitigation measures as a part of the MA process.¹²⁴ Whereas in the EU, it is the applicant for a MA, who is only expected to envisage risk mitigation measures within the E(R)A.¹²⁵ Moreover, such precautionary safety measures within the EU are limited to those taken for the storage of the product, its administration to patients and for its disposal.¹²⁶

Regarding the packaging requirements of medicines, in the EU the MA applicant is required to provide in their application a 'mock up' of the outer packaging.¹²⁷ This must, where appropriate,¹²⁸ include instructions for the disposal of unused medicines or the waste thereof and a reference to the appropriate collection system available in that Member State.¹²⁹ In the US, the MA applicant is also required to provide a specimen of the proposed labelling, however there is no specific requirement to inform patients about the correct way to dispose of expired or unused medicines. Alternatively, this information is provided to patients via a website maintained by the FDA.¹³⁰

While the legal tools within the EU and US are designed differently, the scope of medicines exempted from the E(R)A requirement is almost the same. However, when weighing up the pros and cons of both the EU and US approach to PiE, there are some factors which favour the US solution. Firstly, the authorities can refuse authorisation of a drug because of a missing environmental impact assessment. Secondly, despite the large number of categorical exclusions, the FDA can still require an E(R)A in exceptional circumstances.

3. Assessment panels and public access to information

When it comes to assessing the data and information gathered by the applicant within the pharmaceutical regulatory processes, it becomes relevant the types of expertise available within the panels which consider the application. US law requires the panel members to come from a variety of technical backgrounds, including expertise in biological and physical sciences.¹³¹ They must nominate members who have experience in the different stages of the medicine's lifecycle,¹³² and they require a panel member who represents the interests of consumers and the pharmaceutical manufacturing industry.¹³³ In addition, scientific organisations have the opportunity to nominate individuals for appointment to the assessment panel.¹³⁴

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¹²³ Ibid., 142.

¹²⁴ CFR part 25.40(e).

¹²⁵ Directive 2001/83/EC, Art. 8(3)(ca).

¹²⁶ Directive 2001/83/EC, Art. 8(3)(g).

¹²⁷ Directive 2001/83/EC, Art. 8(3)(j).

¹²⁸ The EMA has interpreted this as situations when 'the possibility of environmental risks cannot be excluded,' see EMA Guidelines, 9.

¹²⁹ Directive 2001/83/EC, Art. 54(j).

¹³⁰ 21 U.S.C. § 355(r)(2)(F).

¹³¹ 21 U.S.C. § 355(n)(3)(B). The regulation mentions expertise in the fields of "clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences."

¹³² 21 U.S.C. § 355(n)(3)(A). For example, in development, manufacture and use of medicines.

¹³³ 21 U.S.C. § 355(n)(3)(C).

¹³⁴ 21 U.S.C. § 355(n)(3).

Under EU law, the EMA is responsible for forming the advisory panels which consider the MA under the centralised procedure.¹³⁵ The Pharmacovigilance Risk Assessment Committee (PRAC) must consist of members with expertise in pharmacology and pharmacoepidemiology, a representative of healthcare professionals and a representative of patient interests.¹³⁶ The PRAC is expected to contain members with the highest level of qualifications and from a broad spectrum of interests, however ultimately members are appointed on the basis of their expertise in pharmacovigilance and risk assessment of medicinal products for human use.¹³⁷ Furthermore, the Committee for Medicinal Products for Human Use (CHMP), which evaluates the MA application, does not require members to have expertise in the area of environmental risk assessment.¹³⁸ By comparison, the US takes a more inter-disciplinary approach and has a wider range of stakeholders. Whereas, the EU is more focused on members with experience concerning the effects of medicines upon humans through the use of medicines. The rules for nominating members of the PRAC do not require experience in the different stages of the medicine's lifecycle.

In both the EU and US, the presence of expert advisory committees is a common feature in policy-making, with their mission being "to ensure the scientific reliability of policy choices."¹³⁹ However, there have been several scares on both sides of the Atlantic which caused the public to question the expert assessments which support policy decisions.¹⁴⁰ In particular, Europeans were alarmed by the illegal use of growth hormones in meat for human consumption. The policy decisions and trans-Atlantic trade dispute¹⁴¹ which followed, revealed a difference in how EU and US policy-makers understood and engaged with science while setting risk regulations. According to Hornsby, the EU institutions were unable to agree about how to manage the risk of growth hormones used during beef production, so they took a no-risk approach and cherry-picked the scientific evidence to support their decision.¹⁴² This risk management strategy was taken despite most scientists agreeing that growth hormones in meat do not pose a risk to human health.¹⁴³ By contrast, the US policy makers were more willing to trust international scientific bodies, such as the Codex Alimentarius, to correctly assess and set the appropriate level of risk for hormone fed meat.¹⁴⁴

¹³⁵ Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [2004] OJ L 136, Art. 55. The Committee for Medicinal Products for Human Use (CHMP) evaluates the MA application, with the support of the Pharmacovigilance Risk Assessment Committee (PRAC), which provides input related to risk management, and the Committee for Advanced Therapies (CAT) on advanced therapy medicines. NB different rules will apply within each Member State for products registered under the decentralised, mutual recognition and national procedures.

¹³⁶ EMA, 'Pharmacovigilance Risk Assessment Committee Rules of Procedure' EMA/PRAC/567515/2012 Rev.1, Art. 1(1).

¹³⁷ Ibid., Art. 1(2).

¹³⁸ BIOIS Report, supra, note 9, 196.

¹³⁹ Jasanoff, supra, note [Fejll Bogmærke er ikke defineret.Fejll Bogmærke er ikke defineret,16](#), 373.

¹⁴⁰ For example, in the EU during the 70's it was discovered that DES (dethylstilboestrol) was illegally used in veal production in France, which caused hormonal irregularities in adolescents. Consumers reacted by calling for a boycott of veal. WTO Panel Decisions EC v US, para. 2.22. Jasanoff, supra note [Fejll Bogmærke er ikke defineret.Fejll Bogmærke er ikke defineret,16](#), 368. The US has taken a more cautious approach to stem cell research and cloning than the EU, as seen by President Bush's decision to limit funding for stem cell research in 2001 and the House of Representative's ban in 2001 on all forms of cloning, Jasanoff supra note 16, 364-365.

¹⁴¹ US - EC Measures Concerning Meat and Meat Products, supra note [181824](#); Report of the Appellate Body, EC Measures Concerning Meat and Meat Products (Hormones), supra note [181824](#), para. 2.26.

¹⁴² The EU Commission did not consider growth hormones as a health risk, whereas the Council and the Parliament did consider them a health risk, Hornsby, supra note [120120119](#), 138.

¹⁴³ Ibid., 139.

¹⁴⁴ Ibid., 138.

The WTO panel established to settle the trade dispute between the EU and US, focused upon the method by which the EU established the level of risk it considered appropriate to protect its citizens from hormones in meat.¹⁴⁵ The panel agreed with the US approach, in that the appropriate level of risk should be applied in a consistent manner in line with the provisions of the Sanitary and Phytosanitary (SPS) Agreement, not upon consumer's perceptions of that risk.¹⁴⁶ It is interesting to note Norway's submission before the panel. Norway argues it is a sovereign right to determine the level of risk deemed appropriate for the protection of its citizen's health and the measures appropriate to achieve this risk.¹⁴⁷ They contend that nations do not have "to scientifically prove the extent of the risk," only show that a risk existed. It was then for the nation "to define the level of probability of harm it wanted to assume."¹⁴⁸ The difference in the EU and US approach to the role of science in setting risk management measures is interesting because it highlights the different views on what is sufficient science and the inherently political nature of E(R)As.¹⁴⁹

In relation to the disclosure of information to the public gathered for the purpose of E(R)A during the pharmaceutical regulatory processes, the US and EU differ only slightly in their approach. Both jurisdictions ensure a data protection (and data exclusivity) period to MA applicants of original medicines.¹⁵⁰ This means data submitted with the MA application cannot be relied on by another applicant, primarily by an applicant for a generic product's MA before the data protection period expires. The rationale behind providing this special type of intellectual property right to medicines is the high costs and risks associated with the development of a new product. The data protection thus has introduced a right parallel to patent protection, in order to support innovation in the pharmaceutical sector. Moreover, confidential environmental data can be protected as a trade secret.¹⁵¹ In order to secure proper data protection within the US context, the law distinguishes between confidential and non-confidential parts of data submitted with the E(R)A.¹⁵² The confidential data must be summarised in the E(R)A to the extent possible, but will not be disclosed in full to the public.¹⁵³ Non-confidential information shall be made available to public upon request.¹⁵⁴

Similarly to the US, in the EU context, the EMA does not publish results of E(R)As in full, but only the non-confidential parts, such as the fate and effects endpoints of human and veterinary pharmaceuticals, in a standardized format.¹⁵⁵ The results of E(R)A are made available to public within so-called European Public

¹⁴⁵ *US - EC Measures Concerning Meat and Meat Products (Hormones)*, supra note [181821](#). See e.g. para 8.140 "The United States argues that the European Communities has never performed an appropriate assessment of these alleged risks and has, in any event, not relied on, nor put forward, any assessment of these risks that could serve as a basis for the EC ban."

¹⁴⁶ *Ibid.*, paras 8.165 and 5.28. The measures should be based upon in particular Articles 2, 5.2, 5.3, 5.4, 5.5 and 5.6 of the SPS Agreement.

¹⁴⁷ *Ibid.*, para 5.18. They argue this is an established principle under Art. XX(b) of the GATT Agreement.

¹⁴⁸ *Ibid.*, para 5.19.

¹⁴⁹ For a resume of the academic debate concerning the reasons for this trans-Atlantic divide, see Hornsby, supra, note [120120119](#), pp 4-6.

¹⁵⁰ Directive 2001/83/EC, Art. 10; 21 U.S. Code § 355. While the data protection period lasts for 8 years and the market exclusivity period for another 2 years within the EU, the data protection period within the US lasts for 5 years only. This is justified by the possibility to prolong patent protection for pharmaceuticals for 5 years.

¹⁵¹ CFR part 25.50(b); Directive (EU) 2016/943 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure, [2016] OJ L 157.

¹⁵² CFR part 25.51(a); see also U.S. Guidance for Industry, supra, note [424245](#), pp 26-27.

¹⁵³ CFR part 25.51(a).

¹⁵⁴ CFR part 25.52(b)(2).

¹⁵⁵ Anette Küster et al., 'Pharmaceuticals in the environment: scientific evidence of risks and its regulation' (2014) 369 *Philos Trans R Soc Lond B Biol Sci.* (1656), 6.

Assessment Reports (EPAR), which describes them in language understandable to public.¹⁵⁶ The EMA does not require an applicant for an MA to distinguish between confidential and non-confidential parts of the data. This leads to the situation where the format of EPARs is standardised, but the content is not. The result is a highly non-transparent situation, with the duplication of environmental test data (including animal testing) as each applicant has to generate their own data set, and frequent inconsistencies in E(R)As' results.¹⁵⁷

Experts have been calling for the EU to amend the law and make scientific data gathered during the MA more readily available to the general public and professionals.¹⁵⁸ This would firstly allow greater access to information about the safety and efficacy of the drug and, thus, promote more informed public debate about the risks and benefits of pharmaceuticals. Secondly, it would be helpful for MA applicants when preparing their E(R)A when identifying knowledge about the respective API. This would support consistency between E(R)As, allow increased learning and avoid duplications in testing.¹⁵⁹ However, the protection of intellectual property rights stand in the way of implementing this increased transparency. Implementation of such data publication and sharing would therefore need legislative changes.¹⁶⁰ Yet, recent case law of the Court of Justice of the European Union broadened up the possibility to request more MA related information within the current legal framework.¹⁶¹ This is a positive development towards securing public access also to E(R)As' results. The three cases discussed, among others, the scope of commercially confidential information. The court noted that in order for information to be considered commercially confidential, the respective company must provide concrete evidence how would the disclosure of the information specifically undermine their commercial interests.¹⁶²

In summary, public access to information gathered during the E(R)A process is low in both the US and the EU. The US gives the public access to the environmental data, by allowing the disclosure of all the non-confidential part of the E(R)A upon request. Meanwhile, within the EU the EMA decides which data from the non-confidential information is included in published EPARs. Moreover, the possibility of access upon request within the EU context is limited, but developing in a positive direction, at least in respect to centrally registered products. In respect to products registered via other procedures, a better utilization of the Directive 2003/4/EC on public access to environmental information to access non-confidential parts of data gathered for E(R)A could also be a possibility.¹⁶³ For now, the possibility to use the directive and allow for public access to the E(R)A data upon request is limited due to the broad definition of 'commercial

¹⁵⁶ Regulation No. 726/2004, Art. 13(3).

¹⁵⁷ Agerstrand et al., supra, note [595962](#), 5339.

¹⁵⁸ BIOIS Report, supra, note 9, pp. 180-183; Agerstrand et al., supra, note [595962](#), 5337; Caneva. et al., supra note [505053](#), pp 312-316.

¹⁵⁹ A pilot open-access database of ecotoxicity data for pharmaceutical substances has been established in Sweden <www.mistrapharma.se/wikipharma-13497291> accessed 21 December 2017.

¹⁶⁰ EMA, 'Concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 corr 2' (2016) EMA/CHMP/SWP/65429/2016, <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500205987.pdf> accessed 19 December 2017.

¹⁶¹ Case T-235/15, *Pari Pharma v EMA*; Case T-718/15, *PTC Therapeutics International v EMA*; Case T-729/15, *MSD Animal Health Innovation and Intervet international*.

¹⁶² EMA, General Court confirms EMA approach to transparency, Three rulings clarify the scope of commercial confidentiality with regard to authorised medicines, 6 February 2018, EMA/73690/2018.

¹⁶³ Directive 2003/4/EC on public access to environmental information, [2003] OJ L 41, Art. 7(2)(g).

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confidential information’,¹⁶⁴ which allows for refusal to render the sought information.¹⁶⁵ However, as the recent case of the CJEU shows, this broad definition is getting tighter. Still, the main reason for the limited environmental data availability remain the protection of intellectual property rights, in particular the trade secret and data protection as mentioned in the discussion above.

IV. Conclusion

Scientific evidence regarding the possible harmful effects of medicines to the environment, and arguably also to human health, have led legislators in both the EU and the US to implement environmental concerns into the field of pharmaceutical law.

When balancing the risks and benefits of new medicines, both the US and EU require applicants to submit an E(R)A during the MA procedure. However, only the US takes into account the E(R)A results during the risk-benefit analysis. In the EU, it is considered necessary to exclude the E(R)A results from the risk-benefit analysis in order to protect patient health and the competitiveness of the EU pharmaceutical industry. Therefore, the US approach shows a way to weigh up the environmental risk of new medicines alongside the possible therapeutic benefits and thus may provide inspiration to EU legislators.

However, regarding the scope of the E(R)A, although the legal tools within the EU and US are designed differently, the scope of medicines exempted from the E(R)A requirement is almost the same. The broad categorical exclusions within the US law question the effectiveness of the environmental protection and so do the above-discussed limitations of the EU law. Although the goals and the scope of covered products in the two jurisdictions are similar, there are notable differences in what’s considered during the E(R)A. For example, the EU requires the special consideration of endocrine disrupting substances and GMOs. Whereas the US considers the cumulative impact and the effect of manufacturing effluent upon endangered species and ecosystems, including outside of the US. This difference in scope suggests a difference in values and the level of risk deemed acceptable.

In addition, the US and EU both take the approach of managing the impact of pharmaceuticals in the environment by assessing the impact of a particular medical product, not for the API within the medicine. However, the US, unlike the EU, requires applicants to consider the cumulative impact of the medicine within the E(R)A.

In discussing the gaps in our scientific knowledge about the effects of pharmaceuticals in the environment, we highlighted several regulatory challenges which are shared by the US and EU to a certain extent. In both the EU and US, the public lack access to sufficient scientific data about the presence of pharmaceuticals in the environment, firstly because of a lack of testing for the presence of pharmaceuticals in the environment and secondly because data generated during the MA procedure is protected by intellectual property rights. However, the US does allow the release of non-confidential data to the public upon request. In the EU, non-confidential parts of the data are reported within EMA’s European Public Assessment Reports. Each approach carries certain problems with them. The US solution relies on an active effort of the public to demand access to the data, since they have to file a request. In the EU, it is only preselected data that are

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¹⁶⁴ European Medicines Agency policy on access to documents (related to pharmaceuticals for human and veterinary use), Policy/0043, effective on 1 December 2010, Doc. Ref. EMA/110196/2006 (“any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information.”) NB the policy has been revised and open for public consultation in February 2017 (EMA/729522/2016).

¹⁶⁵ Directive 2003/4/EC, Art. 4(2)(d).

presented in a standardised form by the EMA and, thus, there is no certainty that the data are comprehensive or even representative.

Both the US and EU seek to include more environmental interests into the regulatory processes through forming of assessment panels with members with a wide field of experience. By including members from different stages of the medicine's lifecycle and different fields of science, the US arguably comes closer to this objective than the EU.

Another underlying difference between the US and EU approach to risk assessment is the use of scientific knowledge during decision-making. The WTO hormones panel decision put on display the difference in this approach, with the US arguably taking a more objective, science-based approach to assessing the risk.

Obiter dictum from the ECJ's *Pfizer* decision shows risk assessment to be a more political exercise.¹⁶⁶

However, within the risk-benefit analysis of the MA procedure, both the EU and US decision-makers require a high level of scientific data, which plays a deciding role in the approval of a new medicine. Unfortunately, in the EU, this scientific data only concerns the efficacy, safety and therapeutic benefit of the medicine, not the potential environmental impact, as in the US case. Therefore, in the case of the risk assessment of PiE, values play a role in determining the type of scientific data presented before decision-makers in both the EU and US, which can partially explain the different approaches to risk assessment.

This article aimed to compare the letter of the law in the EU and the US concerning the inclusion of environmental concerns into the pharmaceutical regulatory processes. Further work needs to be done to understand all the underlying values in the two jurisdictions driving the legislative work in this area in order to be able to design appropriate and effective laws. Especially the balance between public health concerns and environmental protection might need to be reconsidered in the light of the growing evidence on the detrimental effects of medicines' residue in the environment on human health. While the main focus on human health might be difficult to change, environmental protection in pharmaceutical legislation might be strengthened through reflecting on the indirect effect of medicines' residue on human health through the environment. We hope that our work may serve as evidence and provoke discussion around the conceptual differences between the US and EU regarding the relationship between public human health and environmental protection.

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¹⁶⁶ See relevant discussion on the case in Part II., section 1 above.