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1 **Regulatory Science and Innovation Programme** 2 **for Europe (ReSciPE): a proposed model**

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23 **Abstract**

24 Regulatory science underpins the objective evaluation of medicinal products. It is therefore imperative
25 that regulatory science and expertise remain at the cutting-edge so that innovations of ever-increasing
26 complexity are translated safely and swiftly into effective, high-quality therapies. We undertook a
27 comprehensive examination of the evolution of science and technology impacting on medicinal
28 product evaluation over the next 5-10 years and this horizon-scanning activity was complemented by
29 extensive stakeholder interviews, resulting in a number of significant recommendations. Highlighted
30 in particular was the need for expertise and regulatory science research to fill knowledge gaps in both
31 more fundamental, longer-term research, and with respect to technological and product-specific
32 challenges. A model **is proposed** to realise these objectives in Europe, comprising a synergistic
33 relationship between the European Medicines Agency (EMA), the European Medicines Regulatory
34 Network **and academic** research centres to **establish a novel** regulatory science and innovation
35 platform.

36

37 What is already known about this subject?

38 The EMA and medicinal product regulators around the world, are confronted continuously with
39 advances in science and technology. However, the complexity of innovation is increasing rapidly,
40 requiring regulatory science to evolve in tandem and to develop an effective mechanism to do so in a
41 timely manner.

42

43 What this study adds?

44 This study explores regulatory science needs over the next 5-10 years and proposes a mechanism to
45 enable regulatory science to keep pace with innovation.

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48 Introduction

49 Translating fundamental science into patient-accessible therapies requires application of diverse
50 scientific disciplines. Regulatory science underpins the objective evaluation of the safety, efficacy and
51 quality of medicinal products and crucially informs the regulatory decision-making process.

52 Specifically, therefore, regulatory science must provide medicines' regulators with the knowledge to
53 apply innovative research and novel methodological tools to the objective determination of the
54 benefits and risks associated with the use of a new medicinal product¹. It is fair to say, however, that
55 rapid progress in the biomedical and related sciences – for example, in areas such as cell-based
56 therapies, drug-device combinations, predictive toxicology and artificial intelligence – mean that the
57 most challenging regulatory questions²⁻⁴ are originating from the fastest moving and most competitive
58 scientific disciplines⁵. As a result, it is absolutely imperative that regulatory science remains at the
59 cutting edge so that innovations of ever-increasing complexity are translated safely into efficacious
60 and affordable therapies in a timely fashion, promoting public health.

61 The European Medicines Agency (EMA) engages continuously with advances in regulatory science and,
62 in 2017, undertook a comprehensive baseline review examining the evolution of science and
63 technology that will impact its core business of medicinal product evaluation over the next 5-10 years.
64 This horizon-scanning activity was complemented by an extensive stakeholder outreach exercise
65 across individuals and organisations involved in the entire medicine development lifecycle (and
66 included, *inter alia*, the pharmaceutical industry, health technology assessors and payers, regulatory
67 science experts, academia, scientific organisations and societies, European Union research
68 infrastructure networks, healthcare professionals and patient representative groups). The cumulative
69 result of this concerted effort was a document⁶, “EMA Regulatory Science to 2025 – Strategic
70 Reflection”, currently released for public consultation at the end of 2018 and recently summarised in
71 the literature⁷. A key component of this reflection is a proposed model to strengthen regulatory
72 science and innovation in Europe, the elaboration of which is now described⁶.

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74

75 **Methods**

76 1. Horizon scan (baseline review)

77 The initial (>60) areas of review (see Supplementary Information, Table S1) across health, science,
78 technology and regulatory science were selected by the EMA's internal scientific leadership, the
79 Scientific Coordination Group (SCG). Subsequently, a multidisciplinary research group conducted an
80 initial horizon scanning exercise. This included mining, *inter alia*, internal databases and the relevant
81 scientific literature. In each area reviewed, the state-of-play and the projected opportunities and
82 challenges over the coming 5-10 years were identified. These results were authenticated within the
83 research group, and then peer-reviewed by in-house experts and the SCG.

84 2. Stakeholder interviews

85 Interviews were then carried out with external experts and key opinion leaders from the EMA's
86 principal stakeholder groups to validate the internal conclusions. Interviewees were nominated by the
87 European Medicines Regulatory Network (EMRN) and drawn from the Agency's expert database; non-
88 response error was mitigated through follow-up reminders. The interviews (n = 70) were either semi-
89 structured (55) or open (15). The stakeholders were provided with a series of key questions
90 (developed by the research group) and an introduction to the baseline review prior to the interviews.
91 The questions were aligned with the aims of the regulatory science reflection and were trialled with
92 colleagues, and re-ordered and optimised in terms of timing. The resultant draft script was then tested
93 on an initial panel of interviewees for feedback. This feedback was incorporated into a final master
94 script⁷ targeted towards semi-structured interviews with each stakeholder group. For the open
95 interviews, the script was used after the interviewees had provided their unprompted, initial topics
96 for discussion.

97 3. Data acquisition and analysis

98 The semi-structured interviews lasted around 1 hour, the open interviews up to 2 hours. A written
99 record of the interviews was made by two or more of the research team and then cross-checked for
100 accuracy and consistency. Analysis of the information obtained involved open and axial coding^{8,9}
101 whereby the research team attributed codes to meaningful sections of text (words, statements and
102 sentences). These codes were compared and a subset agreed before undertaking additional rounds
103 of axial coding. The findings were eventually reported using Consolidated Criteria for Reporting
104 Qualitative Research (COREQ)¹⁰. Finally, the codes were grouped into themes, which were compared
105 to and merged with the results of the horizon scan and baseline review. From this exercise, a set of
106 overarching strategic goals for regulatory science emerged along with a number of core
107 recommendations and associated underlying actions necessary to achieve these aims.

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109

110 **Results**

111 The baseline review, horizon scan and stakeholder outreach resulted in over 600 comments and
112 recommendations. Many of these identified the need for expertise and regulatory science research
113 to fill knowledge gaps in two broad areas as discussed in detail in the published EMA document, “EMA
114 *Regulatory Science to 2025 – Strategic reflection*”⁶ and summarised elsewhere⁷: (i) those requiring
115 more fundamental, longer-term research, and (ii) where technology or product-specific challenges
116 were evident. Relatedly, the limited funds available for regulatory science research, and the clear need
117 for more resource in this area, represented very strong signals.

118 Regarding expertise, a deficit in the area of regulatory science know-how was identified, particularly
119 in rapidly evolving domains of research and innovation⁶ such as drug-device combinations, predictive
120 toxicology and artificial intelligence. A more proportionate approach to access international expertise
121 was a recurring suggestion in this regard. Enhanced training in the relevant science for stakeholders
122 and regulators alike was also highlighted.

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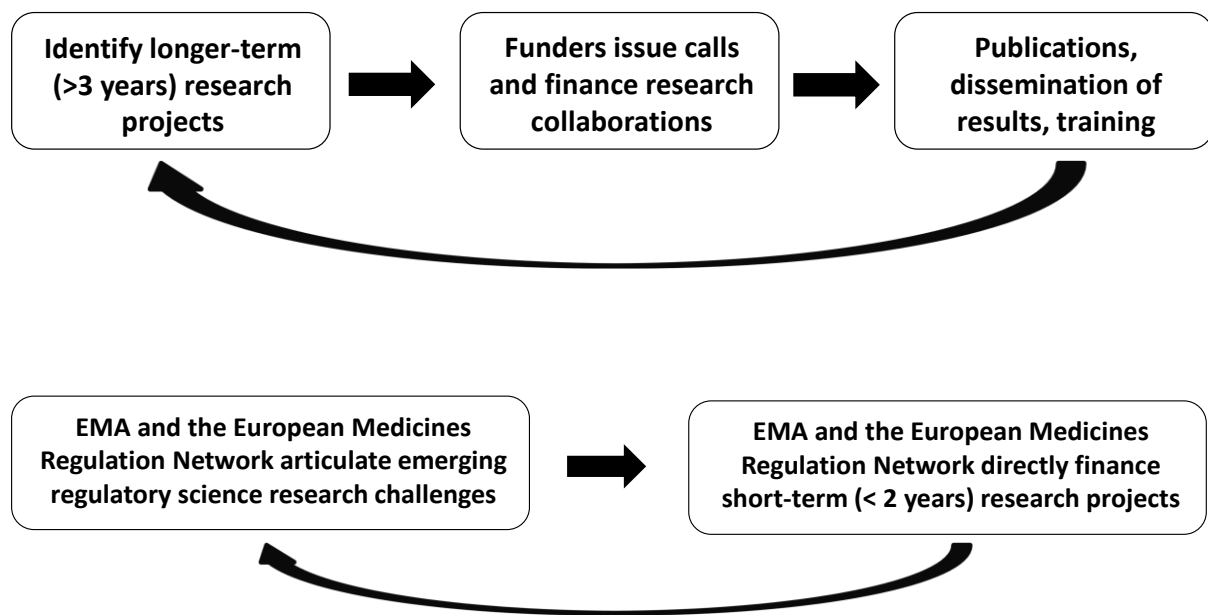
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141 Discussion

142 The primary role of medicines regulatory agencies may be summarised as one of protecting and
143 promoting public health and, increasingly, by catalysing and enabling science to be translated into
144 patient-centred healthcare¹. To meet these objectives, the regulatory agency must understand the
145 fundamentals of the relevant science, and their application in the medicinal product review and
146 approval process, and be critically informed of key areas of scientific innovation that have the
147 potential to impact on its core business^{5,6}.

148 **A model to underpin regulatory science and innovation in Europe**

149 A mechanism with which these goals can be achieved in Europe is a synergistic relationship between
150 the EMA, the EMRN and distributed academic research centres to establish a novel science and
151 innovation platform – provisionally termed the Regulatory Science and Innovation Programme for
152 Europe (ReSciPE) – that undertakes both long-term, fundamental research in strategic areas of
153 regulatory science (Figure 1, upper panel), and shorter-term investigations to address emerging
154 regulatory science questions (Figure 1, lower panel).



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158 **Figure 1:** Upper panel - An iterative partnership between regulators, European public funding agencies
159 and academic scientists to strategically focus basic research in regulatory science. **The potential**
160 **funding agencies include those at the European level, such as DG RTD and IMI, and national funders.**
161 Lower panel - Research collaboration between network scientists and academia to tackle rapidly-
162 evolving regulatory science questions and to translate innovation efficiently into regulatory tools and
163 processes.

164 **ReSciPE: goals and deliverables**

165 It is anticipated that ReSciPE will identify research priorities that promote the field of regulatory
166 science - including innovative research, development of regulatory tools, education, and scientific

167 exchange - together with not-for-profit and commercial entities striving to produce safe, effective,
168 affordable and high-quality medical products. Self-evidently, collaboration involving ReSciPE and the
169 European pharmaceutical, biotechnology, and high-tech industries is particularly important to the
170 long-term aims articulated above. With the governance of these collaborations being carefully
171 decided by funders at the call stage. It is also envisaged that partnerships between EMA, the EMRN
172 and academia will also develop regulatory training modules and undertake horizon scanning in
173 emerging areas of innovation, and that ReSciPE will drive a data-sharing culture to foster open science
174 that is mutually beneficial for all stakeholders.

175 *Precedence for success in Europe*

176 Given the strength of the pharmaceutical and biotechnology industries in Europe, **the established**
177 **importance of leading scientific professional societies (such as EUFEPS, the European Federation for**
178 **Pharmaceutical Scientists)**, the considerable regulatory expertise at EMA and across the EMRN, and
179 the world-leading quality of biomedical research related to medical product innovation and
180 development in European universities and research centres, the present situation also affords a real
181 opportunity to accomplish a paradigm-shift in regulatory science and innovation through the
182 establishment of ReSciPE⁶. This concept must build upon precedents at the national level, including
183 the Dutch Medicines Evaluation Board (MEB) Regulatory Science Program, which has led to the
184 creation of a broad network of partnerships between academic and other external parties¹¹. In this
185 way, MEB has committed a budget to catalyse and facilitate both short-term projects and longer-term
186 PhD theses to enhance its ability to deliver high quality benefit/risk assessment. Three specific areas
187 of the medicinal product lifecycle have been targeted: development and innovation, regulation and
188 decision-making, and consumer use and safety. At the same time, MEB is actively participating in
189 regulatory education and learning, for example, via internships to bachelor- and masters-level
190 students. Other similar research models include Germany's Federal Institute for Drugs and Medical
191 Devices (BfArM)¹², which conducts research in collaboration with national, EU and international
192 research centres and academia, and the Paul-Ehrlich-Institut, (PEI)¹³, which interacts with leading
193 research institutes, academia and international organisations to set new standards in the field of
194 vaccines/biomedicines. Another example is the European Center of Pharmaceutical Medicine
195 (ECPM)¹⁴, based at the University of Basel, that provides training which covers the entire medicinal
196 product development process from molecule identification to commercialisation, including an
197 understanding of essential aspects of regulatory science.

198 Most recently, a new EU-funded project entitled "Strengthening Training of Academia in Regulatory
199 Science" (STARS)¹⁵, was initiated. The consortium involved includes the EMA and 20 regulatory bodies.
200 The three-year project aims to analyse and improve the training of academia in regulatory science and
201 to enhance regulatory protocol assistance in academic-driven health research. These measures are
202 designed to facilitate translational clinical research in academia, and to accelerate the availability of
203 innovative, cutting-edge therapies to patients across Europe.

204 *CERSIs: an American model*

205 Furthermore, evidence from the US, in particular, suggests that this model of synergistic partnership
206 between a regulatory agency, academic researchers and key stakeholders, such as established
207 pharmaceutical companies and small and/or medium-sized enterprises, is a fruitful approach to
208 ensure that research ideas are effectively translated into new and effective medical products and that

209 technological advances resulting in novel tools are applied to catalysing and facilitating the regulatory
210 review and approval process, thereby accelerating patient access to innovative therapies¹⁶. The US
211 Food & Drug Administration (FDA) currently funds five Centres of Excellence in Regulatory Science &
212 Innovation, each with a particular focus associated with the Agency's priority areas¹⁷. The UCSF-
213 Stanford Centre, for example, is addressing the over-arching strategic aim to develop new models and
214 methods for moving drugs and other medical products, such as devices and cell-based therapies, from
215 the laboratory to clinical trials¹⁸. In parallel, the Centre provides training and educational programs
216 (including internships and laboratory rotations) for PhD students, postdoctoral fellows, faculty and
217 scientists in the industry and at the FDA.

218 **Conclusions**

219 Scientific challenges in regulatory science and innovation span the entire spectrum of the medicinal
220 product lifecycle – for both human and veterinary drug product development¹⁹ – from, for example,
221 the conception and development of new cell-based treatments, through new thinking in predictive
222 toxicology, and the rapidly increasing variety of imaginative drug-device combination products, to new
223 ideas concerning the personalisation and precision of medical therapy (including the manufacturing
224 challenges)^{5,6}. As such, there is a strong rationale for ReSciPE to use a distributed model, and to
225 benefit from the collaboration of expertise across different academic centres that each concentrate
226 on specific target areas of investigation.

227 The scale of investment required is logically a function of the number and complexity of the
228 transformational research questions to be addressed, the requirements for associated infrastructure,
229 and the perspective taken on the specific role of ReSciPE in training early-career scientists in this
230 important field. In developing existing interactions between the EMA, the EMRN and academia (as
231 well as integrating with ongoing key European activities as mentioned above) to ensure that
232 regulatory science keeps up-to-date, these resources must also be proportional to the public health
233 aim of ensuring that medicines' regulation not only guarantees safe and effective therapies that meet
234 the highest standards of quality, but that it also facilitates patient access to these innovative and
235 important medicines⁶. While this latter challenge is one with which regulators are wrestling to an
236 ever-increasing extent, further discussion of how to achieve better and more uniform access to novel
237 (and almost always expensive) therapies, and to a high standard of healthcare in general, is beyond
238 the scope of this article.

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242 understood or quoted as being made on behalf of or reflecting the position of the agencies or
243 organizations with which the authors are affiliated.

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