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Regulation, innovation and disruption: the European Medicines Agency and adaptive licensing of pharmaceuticals

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Abstract

Growing concerns over the related problems of more speedily bringing innovative pharmaceuticals (especially so-called ‘precision medicines’) to market, and addressing areas of unmet medical need, have engendered critical scrutiny of the existing process for the licensing of pharmaceutical products. The objective is to enable these products to receive approval sooner, but on the basis of the provision of less complete evidence, than was previously the case. This article examines the attempts made to tackle this issue at European Union level, through a pilot programme exploring ‘adaptive’ approaches to licensing operated by the European Medicines Agency. Responses to this initiative indicate significant difficulty in securing regulatory legitimacy in this context. This suggests that innovative pharmaceutical technologies are disruptive of existing regulatory frameworks, such that future attempts to accommodate them within these may be susceptible to failure.

Pharmaceuticals; licensing; European Medicines Agency; legitimacy; disruption.

Introduction

The point at which a medicine is licensed, or granted market authorisation, while merely a ‘snapshot’ in its lifespan, is nonetheless a ‘crucial’ stage in its development. It can be seen as a ‘magic moment’ of transition, at which the substance morphs from an object of scientific experimentation accessible only to a small number of preselected clinical trial subjects, to a consumer product accessible to millions of patients, albeit that it may not be freely available to such patients without the intervention of a medical professional. This process has traditionally been premised upon a binary approach to knowledge: a medicine is safe or not safe, effective or ineffective, authorised or not. The pre-licensing and post-authorisation stages are thus clearly

1 Emily Jackson, Law and the Regulation of Medicines (Hart Publishing 2012) 73.
distinct and are accordingly governed by differing legal and ethical frameworks.

However, this binary model, and the rigorous standard of evidence of safety and efficacy upon which it is premised, has recently become the subject of attention and revision in a number of jurisdictions. For example, the US 21st Century Cures Act, which became law in December 2016, reforms the process for approval of new medical products by the Food and Drug Administration (FDA), inter alia permitting the use of ‘real world evidence’, ie data derived from sources other than randomised controlled trials, and establishing a ‘limited population pathway’ which allows for regulatory approval to address unmet needs for antibacterial and antifungal medications within limited populations, even if there is a lack of evidence to establish a favourable cost-benefit ratio for the drug in a larger population. In the UK, a new ‘Accelerated Access Pathway’ for strategically important, transformative products, seeks to ‘align and coordinate regulatory, reimbursement, evaluation and diffusion processes to bring these transformative products to patients more quickly’. This might entail conditional recommendation by the National Institute for Health and Care Excellence (NICE) of a drug for use in the NHS, subject to the collection of additional evidence to fully

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3 Public Law 114-255.

4 Section 3022. Randomised controlled trials, seen as the ‘gold standard’ of clinical research, are quantitative, comparative, controlled experiments in which investigators study two or more interventions in a series of individuals who receive them in random order. For further discussion, see Jackson (n 1), 26-29.

5 Section 3042.

demonstrate its value and impact.\textsuperscript{7} Similar initiatives have been adopted or proposed in Canada,\textsuperscript{8} Singapore,\textsuperscript{9} and Japan.\textsuperscript{10}

This article explores the attempts made by the European Medicines Agency (EMA) to move in a similar direction of travel, and the challenges which it encountered in so doing. The experiences of the EMA in this regard afford instructive lessons not only in the pharmaceutical context but also, more broadly, in respect of the regulation of innovative technologies. In particular, they highlight that ‘a fundamental challenge for law and regulation in responding to technological developments concerns the quest for social credibility and acceptability’.\textsuperscript{11}

**The context: pharmaceutical innovation and ‘unmet medical need’**

In order to comprehend why the current binary model of marketing authorisation for pharmaceuticals has come under scrutiny, it is first necessary to outline the industry and consumer (patient) context in which it operates. This section seeks to explain how a commonality of perspectives between these ostensibly differing interests – traditionally associated with swift access to market on the one hand, and efficacy and safety on the other – has emerged to place the established regulatory structure under challenge.

\textsuperscript{7} ibid, para. 2.3.1. An Accelerated Access Collaborative, consisting of representatives of NHS bodies, government departments and industry, and with clinician and patient representation, will designate which products (comprising medical devices, diagnostic and digital devices, in addition to pharmaceuticals) are ‘transformative’ and thus eligible for the Pathway. Significantly for the argument subsequently presented in this article, the first products so designated (in October 2018) are those with full evidence bases already within the system: see <www.nice.org.uk/aac#innovations> (accessed 16 April 2019).


First, from the standpoint of a manufacturer, the number of new active substances approved for marketing by the major regulatory authorities has remained relatively stable in recent years – for example, 38 new medicinal products were approved by the EMA in 2011, and 42 in 2018\(^\text{12}\) – but concurrently the cost of research and development has increased significantly, doubling in Europe between 2000 and 2016.\(^{13}\) Successfully bringing drugs to market has therefore become a more expensive activity, and this – combined with the relatively low proportion of total sales volume which is constituted by recently-marketed products\(^\text{14}\) – has tended to stimulate a cautious business model, characterised by production of significant numbers of ‘me too’ drugs.\(^\text{15}\) These add little therapeutic value to those which are already commercially available, but being similar to compounds which have been demonstrated to be safe and effective, necessitate less investment of time and expenditure upon development and testing and therefore present lower financial risk to pharmaceutical manufacturers and their shareholders.\(^\text{16}\)

The prevalence of ‘me too’ drugs on the market is indicative of shifting paradigms within the pharmaceutical industry. The late twentieth century was marked by significant growth in the industry, fuelled in large part by sales of ‘blockbuster’ drugs (defined as those generating sales in excess of US $1 billion), which constituted more than half of the revenue of major pharmaceutical


\(^{13}\) European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures: Key Data 2017* (EFPIA 2017) 3. The factors underpinning this increase are various, but include more complex and expensive clinical trials, increased failure rates during the development stage, and lengthy development times. These in turn can be explained by risk averse regulation and technological development, factors which are discussed further below. For discussion, see Jorge Mestre-Fernandez, Jon Sussex and Adrian Towse, *The R & D Cost of a New Medicine* (Office of Health Economics 2012).


\(^{15}\) The Association Mieux Prescrire, a not for profit continuing education organisation for healthcare professionals, estimates that approximately half of medicines authorised in the EU between 2006 and 2015 offered ‘nothing new’: ‘New drugs, new indications in 2015: little progress, and threats to access to quality healthcare for all’ (2016) 25(171) Prescrire International 137.

\(^{16}\) See Jackson (n 1), 80.
corporations. However, as many of these drugs lost patent protection in the early 21st century, sales and revenues fell. Some degree of market share could be preserved by developing ‘me too’ variants of those drugs whose patents were about to expire. Nonetheless, such a strategy, while quite financially secure, is not optimal for manufacturers since there is a ‘relationship between high innovative propensity and sustained superior profitability’; moreover, notwithstanding the numbers of such drugs which have received market authorisation, some regulatory bodies have sought to prioritise innovative over ‘me too’ drugs, rendering the latter less attractive to develop.

There is an apparent incentive, therefore, for the industry to seek new directions. One response has been to focus on the development of drugs for ‘orphan diseases’, and there have been significant increases in the number of such drugs granted marketing authorisation in both the US and EU since 2000: the implications of this trend have been analysed elsewhere. The second strategy is to move towards ‘precision (or personalised) medicine’, that is, ‘the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to


21 Within the EU, these are defined as conditions with a prevalence of less than 5 per 10,000 persons.

22 See Viviana Gianuzzi and others, ‘Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen’ (2017) 12:64 Orphanet Journal of Rare Diseases. The increase is also attributable to incentives within the regulatory process, for discussion of which in the EU context, see Keith Syrett, ‘Looking after the orphans? Treatments for rare diseases, EU law and the ethics of costly healthcare’, in Mark Flear and others, eds., European Law and New Health Technologies (OUP 2013).

23 Syrett, ibid.
better individual treatment’. Advances in pharmacogenomics – the study of the influence which genetic factors play in drug response – have facilitated the ‘stratification’ of patient populations into subgroups based upon a common characteristic, which respond better to a particular drug or suffer fewer side effects to treatment. This is advantageous to manufacturers both because costs may be reduced – since clinical trials can be smaller, and attrition rates due to lack of proof of efficacy during the development process are likely to be lower – and because premium prices can be justified on the basis of the complexity of the underlying science and the need to recoup costs against a smaller patient population. The consequence has been a shift from blockbuster to ‘nichebuster’ drugs, of which the best known are the cancer drugs Herceptin (trastuzumab) and Gleevec (imatinib). Importantly, the majority of these drugs are developed for those with severe, life-threatening conditions, especially various forms of cancer.

This brings into view the patient/consumer perspective, which turns upon the existence of widespread ‘unmet medical need’, a term defined by the European Commission as ‘a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected’. For example, the WHO noted in 2013 that ‘although substantial progress has been seen in some therapeutic areas (e.g. cancer, multiple sclerosis, rheumatoid arthritis), there is still growing concern about the inefficiency of the drug

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26 Gibson, Raziee and Lemmens, ibid, 14-15.


28 The term is used interchangeably with ‘unmet clinical need’ and ‘unmet therapeutic need’.

discovery and development process for new medicines for unmet medical needs’. Similarly, one of the primary rationales for enactment of the 21st Century Cures Act by the US Congress was the perceived need to respond to such needs: the House of Representatives Committee Report which accompanied the Bill commented that ‘with 10,000 known diseases, 7,000 of which are rare, and treatments for only 500 of them, it is clear that there is much work to do’. 

The concept of unmet medical need therefore functions as a ‘boundary object’: ‘it bridge[s] the interests, actions, and understandings of actors from different domains’, in this case medicine and industry. Here, it brings together manufacturer and patient/consumer interests, which might otherwise stand in conflict with one another (for example on swift market access versus safety), in pursuit of a common goal: the production and marketing of innovative medical technologies, especially for treatment of urgent medical needs. This is notwithstanding that the motives for such pursuit – the maximisation of profit on the one hand, the relief of suffering and the restoration of good health on the other – are quite distinct. This connectivity is important because it is more likely to catalyse policy change than if pressure were to be exerted upon policy-makers through one source alone. To adopt Kingdon’s ‘policy window’ analysis, the ‘problem stream’ flows more strongly, thus raising the issue higher up the political agenda, as a consequence of the alliance of interests which is constituted by the bridging brought about through the boundary object.

Hence, a juxtaposition of manufacturer and patient/consumer perspectives, mediated through the concept of unmet medical need, can be discerned within recent EU policy on pharmaceuticals. For example, Council Conclusions of 2016, inter alia, note ‘the important role of the life sciences industry in Europe, in particular, in developing effective new treatments for patients with high unmet medical needs’, but also recognise that ‘the exact conditions for the inclusion of innovative and specialised medicinal products in the existing schemes of early marketing authorisation could be further clarified in order to... focus on medicinal products of major therapeutic interest for public health or to meet unmet medical needs of patients’. The steps taken by the EU, and in particular the EMA, in this regard will be outlined in more detail below.


34 Council, ‘Conclusions on strengthening the balance in the pharmaceutical systems in the EU and its member states’ (17 June 2016), [23], [12].
Regulatory defects

Within this significantly changing environment, the existing process for the granting of authorisation for the marketing of pharmaceuticals has been called into question. A variety of perceived deficiencies have been identified.

The fundamental claim is that regulatory authorities have tended towards over-caution, being too stringent in their application of criteria for authorisation, and that this has stifled innovation in the pharmaceutical sector and exacerbated the problem of a failure to meet patient medical needs. This critique originated in relation to the FDA in the 1970s, but similar views have been expressed of the EMA and the WHO has identified it as a global impediment to access to priority medicines. While the exercise of prudence is a familiar theme in the general literature on regulation of innovative technologies, reflecting application of the precautionary principle, the evidence to support such an assessment in the case of pharmaceuticals is, in fact, not wholly conclusive. On the one hand, a study conducted by the EMA found that medicines regulators were ‘perceived risk averse’ ie ‘the more risky an activity was perceived, the less likely they were to engage in it’, and Eichler and others offer anecdotal evidence of instances in which regulators appear to have taken a particularly cautious approach to introduction of new medical technologies. However, the same authors also note that regulators are frequently more willing to authorise new...


37 Kaplan and others (n 30), 14.

38 See eg Roger Brownsword and Morag Goodwin, Law and the Technologies of the Twenty-First Century (CUP 2012) 47-48; Part II.

39 Discussed further below (n 58) and accompanying text.


vaccines than are the public to use them.\textsuperscript{42} In light of this uncertainty, it is likely that the picture is more complex and that some degree of risk aversion on the part of regulatory agencies may combine with conservative manufacturing strategies on the part of pharmaceutical corporations (notably the production of ‘me too’ drugs which are both more likely to receive regulatory approval given similarities to existing compounds which have already gained authorisation,\textsuperscript{43} and less costly to research and develop)\textsuperscript{44} to limit innovation.

However, the broad claim of regulatory risk aversion can be further dissected to delineate specific aspects of the authorisation process which have generated criticism. Two linked dimensions are of particular significance: the temporal and the evidential.

In respect of the first, it is argued that lengthy development times for innovative new pharmaceuticals (which in turn, increase production costs and may encourage manufacturer reliance on me-too technologies as a cheaper alternative) are driven, at least in part, by the stringency of regulatory requirements.\textsuperscript{45} The concern is that a ‘drug lag’, generated by regulatory caution in the face of unfamiliar and potentially unsafe compounds, inhibits early access to potentially life-saving treatments as various regulatory hurdles have to be surmounted.\textsuperscript{46} This temporal problem is exacerbated by the relatively recent interposition of an additional ‘fourth regulatory hurdle’ for pharmaceuticals, subsequent to the granting of marketing authorisation, in the form of health technology assessment (HTA) by means of which the clinical and cost-effectiveness – in effect, the value – of drugs is evaluated.\textsuperscript{47}

\thalign="center"\textsuperscript{42} ibid, 909.

\textsuperscript{43} Although, as noted above (n 20) and accompanying text, certain agencies may disincentivise production of such drugs.


\textsuperscript{46} This argument was especially prominent in relation to FDA approval of drugs, such as AZT, for the treatment of HIV/AIDS: see Daniel Henniger, ‘Drug Lag’ in David Henderson, ed., The Concise Encyclopedia of Economics (Library of Economics and Liberty 1993), available at \texttt{<www.econlib.org/library/Enc1/DrugLag.html>} (accessed 16 April 2019).

\textsuperscript{47} The other three hurdles are quality, safety and efficacy. Clinical effectiveness, as a dimension of HTA, assesses whether the product produces greater health gain than currently available
health systems will encounter difficulties in accessing the treatment as the state (or other payer) will generally not provide reimbursement, even though marketing authorisation has been granted.

The ‘drug lag’ gives rise to particular political problems in situations where patients possess information upon drugs which are in the process of development, for example through patient organisations, manufacturer websites, or social media, as may well be the case where needs for treatment are particularly urgent.\(^{48}\) In such circumstances, demands for timely access to innovative medical technologies will be widely and powerfully voiced and, assuming the commonality of interests between industry and consumers/patients which was outlined in the preceding section of this article, it is the regulatory and HTA agencies which hold the key to granting access.\(^{49}\)

Secondly, a major reason why the regulatory process adds significantly to the development time of new pharmaceuticals lies with the evidential criteria required for the granting of marketing authorisation. In order to comprehend these requirements, it is important first to outline the function of the licensing process as it has traditionally been understood.

Jackson observes that licensing ‘gives the new medicine an official badge of reliability’.\(^{50}\) This reliability rests upon proof of the medicine’s efficacy, safety, and quality.\(^{51}\) These criteria are evaluated with reference to the documentation provided by the manufacturer, which, in the case of the EMA, takes the form of a standardised dossier containing a range of information relating both to the manufacturer and the product, including complete results of pharmaceutical (physico-chemical, biological or microbiological) and pre-clinical (toxicological and pharmacological) tests, and clinical trials.\(^{52}\) Based upon evidence of this type, regulators, including the EMA, seek to make a risk-benefit alternatives.

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\(^{50}\) Jackson (n 1), 73.


assessment of the product when it is placed on the market.\textsuperscript{53} This raises a fundamental question of ‘evidence versus access’.\textsuperscript{54} That is, the height of the evidence bar which is set will determine whether, and how quickly, a new pharmaceutical product will receive authorisation and therefore be made available to consumers (patients) in need: the greater the level of regulatory risk aversion, the greater the amount of evidence which will be demanded.

The issue, therefore, is the degree of uncertainty which is acceptable to the regulator (and, by extension, the public).\textsuperscript{55} Here, it is pertinent to note that contemporary pharmaceutical regulation developed in the wake of the thalidomide scandal,\textsuperscript{56} and that it is therefore ‘aimed (broadly) at the protection of patients as consumers of pharmaceuticals’.\textsuperscript{57} In the EU, and elsewhere, this corresponds with the application of the precautionary principle,\textsuperscript{58} as a means to address ‘development risk. This is the “latent risk” which ‘is not known at the time of approval but may subsequently affect pharmaceuticals’.\textsuperscript{59} This arises as a consequence of the various types of uncertainty which surround pharmaceutical products and which make proof of causality between harm and the drug difficult to establish.\textsuperscript{60} To minimise this risk, pharmaceutical companies are

\textsuperscript{53} Reg. No 726/2004 (n 51), recital (14).
\textsuperscript{55} Eichler and others (n 41), 909.
\textsuperscript{57} Tamara Hervey and Jean McHale, European Union Health Law: Themes and Implications (CUP 2015) 326.
\textsuperscript{58} Article 191 TFEU sets out the principle in relation to the environment. However, the Commission has emphasised that ‘its scope is much wider’, applying when ‘potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty’. Those effects include those to human health: see ‘Communication from the Commission on the precautionary principle’, COM/2000/0001 final.
\textsuperscript{60} For discussion, see Barbara Osimani, ‘Pharmaceutical risk communication: Sources of uncertainty and legal tools of uncertainty management’ (2010) 12 Health, Risk & Society 453, 454-55.
obliged to engage in gradual accumulation of evidence, such that the process of drug development can be ‘defined as the progressive reduction of uncertainty about human responses to a candidate medicine’.\(^{61}\) This takes place through the familiar tripartite pattern of clinical trial phases: phase I evaluating toxicity by reference to a small number of healthy volunteers; phase II assessing efficacy by reference to a control group and involving a few hundred persons; and phase III assessing value in clinical practice, with trial subjects ranging from a few hundred to a few thousand.\(^{62}\)

Under the standard regulatory process, it is only once phase III has been successfully completed that marketing authorisation can be granted. The process therefore yields significant amounts of data to the regulator in an effort to reduce as far as possible the uncertainty that harm will eventuate once the drug is marketed. But it is both expensive and time-consuming for pharmaceutical manufacturers. It has been estimated that the overall cost of conducting the three phases of trials is US $206 million,\(^{63}\) with the duration of the phases standing between 75 and 79 months.\(^{64}\) Moreover, attrition rates are high: the percentage likelihood of progressing from a phase I trial to market launch having been estimated at 11.6%.\(^{65}\) As noted previously, it is difficult to disentangle regulatory factors from strategic manufacturing decisions in determining why innovative pharmaceutical products do not reach the market,\(^{66}\) but it certainly seems plausible that these concomitants of a precautionary approach are likely to have an inhibiting effect.\(^{67}\)

These criticisms of the potentially adverse impact which regulation may have upon innovation and the meeting of unmet medical need are not product-specific, although they have gathered pace in recent decades. This is in part because the ‘low-hanging fruit’ of early medical advances has now been gathered, rendering it more difficult for pharmaceutical companies to generate profit in any event.\(^{68}\) However, they have particular resonance in the context of ‘precision medicine’ for the following reasons.

The most significant impediment of the existing regulatory process and approach in this context is evidentiary. Since ‘precision’ treatments are, by definition, targeted at much smaller, stratified patient subgroups, it is extremely difficult to conduct clinical trials on the scale of, and at a


\(^{62}\) For further discussion, see Jackson (n 1), 23-26.

\(^{63}\) Mestre-Fernandez, Sussex and Towse (n 13), 40. Phase III trials are especially costly because they are larger and more complex. The authors estimate the cost of this stage at $129 million.

\(^{64}\) ibid, 71.


\(^{66}\) See Eichler and others (n 41), 911.

\(^{67}\) See ibid; Osimani, (n 59), 124; Avik Roy, Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials (Manhattan Institute for Policy Research 2012).

\(^{68}\) See Epstein (n 35), 5-6 and the discussion of ‘me too’ drugs in the preceding section of this article.
standard comparable to, those used for conventional pharmaceuticals. Accordingly, there is necessarily less robust data for regulatory agencies to evaluate before reaching a determination that the drug is efficacious, safe and of sufficient quality: that is, there is greater uncertainty as to the nature and scale of the possible risk to human health once the drug is made commercially available. A high level of regulatory risk aversion would mean, therefore, that such treatments would rarely receive marketing authorisation, thus ‘stifling’ innovation and leaving significant areas of medical need unmet.

A related point concerns the generalisability of trial data. Recruitment of a stratified patient subpopulation to a trial – for example, through deployment of predictive biomarkers – may well decrease failure rates for pharmaceuticals as efficacy (especially in phase II, at which the largest percentage of treatments fail) will be easier to demonstrate within a less heterogeneous cohort, this being advantageous to manufacturers as it is likely to decrease the costs and duration of drug development. However, it is less clearly positive for an agency seeking to manage risk, since there remain significant uncertainties as to effects upon wider populations post-licensing. In particular, efficacy in, and possible adverse events for, particular patient groups such as the elderly, those with multiple illnesses, or those taking multiple drug therapies, may not be fully evaluated. Even if those patients fall within the stratified subpopulation, only very few (if any) are likely to participate in the clinical trials.

A third concern, which is especially germane to ‘precision medicine’, stems from the fact that, as noted in the preceding section, the majority of such drugs are presently developed for the treatment of life-threatening conditions, especially cancer. Patients with these conditions are frequently in urgent need of treatment, have no alternative avenues to explore, and may well be supported by active and vocal advocacy groups. While a purely needs-driven approach to licensing is ethically inappropriate since it places insufficient weight on efficacy and safety for future generations of patients in order to confer potential benefits upon those who are currently

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69 See Eichler and others (n 54), 238-39. In particular, randomised controlled trials will be harder to conduct given the complex nature of the conditions which precision medicines are developed to treat, such as the existence of multiple genetic aberrations each of which may affect only very few patients.

70 Defined as ‘a clinical or biologic characteristic that provides information on the likely benefit from treatment (either in terms of tumour shrinkage or survival)’: Antoine Italiano, ‘Prognostic or Predictive? It’s Time to Get Back to Definitions!’ (2011) 29 Journal of Clinical Oncology 4718, 4718.


72 See Eichler and others (n 54), 239.

73 ibid; Osimani (n 59), 128.
suffering,\textsuperscript{74} there is nonetheless likely to be significant pressure to allow early access to promising innovative ‘precision’ treatments rather than to await the outcome of the lengthy linear process of drug development followed by regulatory and HTA approval. Indeed, the emergence, notably in the United States,\textsuperscript{75} of a so-called ‘right to try’ drugs which have passed phase I for those with terminal illnesses, is illustrative of the current potency of this factor.

The EMA response

\textit{(i) Conditional Marketing Authorisation}

Perceived deficiencies such as these have led to previous alterations to the regulatory process for marketing authorisation: for example, the FDA has operated a ‘fast track’ process since 1988 and ‘priority review’ and ‘accelerated approval’ processes since 1992.\textsuperscript{76} ‘Compassionate use’ processes are also commonplace.\textsuperscript{77}

In Europe, EMA operates an accelerated assessment process, which reduces the timeframe for licensing from 210 days to 150, upon provision of justification to the Committee for Medicinal Products for Human Use (CHMP: the Agency’s committee with responsibility for elaborating its opinions on human medicinal products, and which makes determinations on marketing authorisation) that the product is expected to be of major public health interest, particularly from the point of view of therapeutic innovation.\textsuperscript{78} There is also a process for authorisation under exceptional circumstances, which may be utilised in situations where there is a lack of

\textsuperscript{74} See Eichler and others (n 54), 237-38.

\textsuperscript{75} See <http://righttotry.org/> (accessed 16 April 2019). This ‘right’ is not limited to ‘precision medicine’, although given the trends in drug development identified previously, many treatments will be of this type. For critical discussion, see Rebecca Dresser, ‘The "Right to Try" Investigational Drugs: Science and Stories in the Access Debate’ (2015) 93 Texas Law Review 1631.

\textsuperscript{76} Krishnan Chary, ‘Expedited drug review process: fast, but flawed’ (2016) 7 Journal of Pharmacology and Pharmacotherapeutics 57, noting that approximately 28% of all approvals between 2013 and 2015 occurred through expedited FDA processes.

\textsuperscript{77} Referred to as ‘expanded access’ by the FDA: see <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm> (accessed 16 April 2019). In the EU, compassionate use programmes are coordinated and implemented by Member States, with provision of recommendations by the EMA: see Reg. No 726/2004 (n 51), art. 83.

\textsuperscript{78} ibid, art. 14(9).
comprehensive data on safety and efficacy, for example because of the rarity of the condition for which the product is intended, or because it would be contrary to generally accepted principles of medical ethics to collect the data required.79

However, it is through the regulatory tool of ‘conditional marketing authorisation’ (CMA) that EMA has made what was until recently its most comprehensive attempt to address the problems identified in the preceding section. This mechanism, which was introduced in 2006, allows for a renewable marketing authorisation valid for one year, subject to specific obligations imposed upon the licence-holder.80 The process enables EMA to grant a licence on the basis of less comprehensive data than is usually required, on condition that further data is collected through ongoing or new studies. Such data usually relate to efficacy and safety, with requirements (for example) that trials evaluate treatment over a longer period, with lengthier follow-up duration, and/or with larger sample sizes, than was the case with the original application.81 Once such data has been obtained and CHMP’s approval has been confirmed, the conditional approval can be converted into a standard marketing authorisation.

EMA argues that there has been ‘considerable interest among stakeholders’ in the CMA process, but acknowledges that ‘it remains just a small fraction of authorisations granted’.82 In total 30 conditional authorisations were granted over the ten-year period to 30 June 2016: this cumulative figure corresponds to less than one-third of the total number of licences granted by the Agency in just one year (2015).83 Part of the explanation for the low numbers of applications lies in the limited scope of the products which may be eligible for a CMA. Under Article 2 of Regulation No 507/2006,84 the mechanism applies only to ‘medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases’, medicinal products to be used in emergency situations, or orphan medical products. Failure to meet the criteria for granting of a CMA has also led to 22 rejections over the same ten-year period: in all of these cases, the CHMP determined that the risk-benefit balance of the product was not positive.85

79 ibid, art. 14(8).


82 ibid, 37.

83 See EMA, Human Medicines Highlights 2015 (EMA 2016) 1.

84 Above (n 80).

85 ibid, art. 4.1(a): the necessity of a positive risk-benefit balance is set out in Dir. 2001/83/EC (n 52), art. 26.1(a). The other requirements for granting of a CMA set out in art. 4.1 (b) to (d) are
Given these statistics, the Agency’s claim that ‘it has been recognised that conditional marketing authorisation is an important tool for ensuring timely access to medicines in areas of unmet medical need’ appears highly questionable. Rather, the CMA mechanism seems, at best, to resemble a ‘kind of “consolation prize”’ awarded when evidence is incomplete, rather than a comprehensive regulatory response to a changing pharmaceutical environment.

(ii) Adaptive licensing

The establishment of CMA can best be understood as part of growing activity within the EU’s governing institutions, led by the Commission, on the promotion of access to innovative medicines since the turn of the century. In 2001, the Commission set up a High Level Group on Innovation and the Provision of Medicines, which recommended that the EU should ‘consider ways of improving the legislation or the operation of the licensing system to improve the introduction to the market in particular for innovative medicines’. The establishment of CMA was a response to this recommendation. Subsequently, a Communication of 2008 set out the Commission’s ‘vision... to ensure that European citizens can increasingly benefit from a competitive industry that generates safe, innovative and accessible medicines’ and highlighted the importance to public health of ensuring access to state of the art treatments without delays. One practical means by which an attempt has been made to realise this vision is through the Innovative Medicines Initiative, a large-scale public-private partnership between the Commission and the European Federation of Pharmaceutical Industries and Associations, which works ‘to improve health by speeding up the development of, and patient access to, the next generation of medicines, particularly in areas of unmet medical or social need’, especially through the facilitation of collaborative research

likelihood of the provision of comprehensive clinical data; the fulfilment of unmet medical needs; and that ‘the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required’.

86 EMA (n 81), 38.

87 Richard Barker, Bioscience - Lost in Translation? How precision medicine closes the innovation gap (OUP 2016) 117.


89 COM/2008/0666 final.

activities. Additionally, the Commission has established an Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) as a sub-group of the Pharmaceutical Committee, with a specific brief to consider regulatory issues leading to market authorisation, with a view to providing advice on speeding up access to innovative and affordable medicines. The Council and Parliament have also played a role: the former through promulgation of a number of Conclusions which stress the importance of access to innovative medicines as a means of meeting unmet medical need and the consequent imperative to address EU and Member State regulatory mechanisms; the latter by way of the creation of an Interest Group on Access to Healthcare, publication of a Report on EU options for access to medicines, and passage of a related Resolution.

Against this lively backdrop, the EMA’s five-year strategy published in 2010, noted a need to ‘address the regulators’ dilemma of balancing access to market vis-à-vis the need for as complete a data package as possible prior to licensing’. The document observed:

a key issue for regulators will be whether a more “staggered” approval (or progressive licensing) concept should be envisaged for situations not covered by conditional marketing authorisations or marketing authorisations under exceptional circumstances, for instance characterised by a better-defined or more restricted population of good responders, followed by a broadening of the population post-authorisation when more “real-life” data are available.... It should be emphasised that progressive

93 Council, ‘Conclusions on the “Reflection process on modern, responsive and sustainable health systems”’ (10 December 2013); Council, ‘Conclusions on innovation for the benefit of patients’ (1 December 2014); Council (n 34).
97 EMA, Road Map to 2015: The European Medicines Agency’s contribution to science, medicines and health (EMA 2010) 20.
licensing should not lead to a reduced level of evidence for first-time marketing authorisation.\textsuperscript{98}

In order to take this forward, EMA (specifically, its Chief Medical Officer, Hans-Georg Eichler) participated in a collaborative research project ‘with a focus on enhancing regulatory science in pharmaceuticals’, with the Massachusetts Institute of Technology, under the aegis of the latter’s New Drug Development Paradigms programme.\textsuperscript{99} The eventual outcome was the launching of an EMA pilot project, running for thirty months from March 2014, on ‘adaptive licensing’, defined as a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence-gathering to reduce uncertainties followed by regulatory evaluation and licence adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made.\textsuperscript{100}

Through the pilot, EMA sought to foster early and ongoing dialogue on a drug development plan between various stakeholders - including patient organisations, organisations producing clinical guidelines, and HTA agencies and/or payers - as well as the manufacturer and the regulatory agency.\textsuperscript{101} While the specificities of the pathway to market authorisation would vary from product to product,\textsuperscript{102} the general pattern would be that marketing authorisation would be granted on the basis of the existence of a positive benefit-risk balance, but for a more restricted patient population than ‘standard’ cases. Initial grant of a licence would be followed by iterative phases of evidence-gathering – to include so-called ‘real world data’, i.e. that derived from observational studies of use of the product rather than through clinical trials – coupled with adaptation of the marketing authorisation to gradually embrace broader patient populations as the level of uncertainty was progressively reduced through additional evidence generation. If and when the regulator was satisfied that the level of uncertainty had been sufficiently reduced, a ‘full’ licence could be granted, with the requirements for ongoing evidence collection eased from that point.

\textsuperscript{98} ibid, 21.


\textsuperscript{100} Eichler and others (n 2), 428.

\textsuperscript{101} See EMA, ‘Questions and answers following the initial experience of the Adaptive Licensing Pilot project’, EMA/417706/2014 (10 September 2014) 1.

\textsuperscript{102} Eichler and others (n 2), 428.
EMA’s eligibility criteria for the pilot related primarily to characteristics of the drug development programme rather than to the product itself. It was specified that applicable programmes should be iterative in character, provide scope for ‘real-world’ monitoring, and have capacity for engagement with multiple stakeholders at various stages along the development pathway. However, there was an acknowledgment that drugs for treatment of certain conditions would be more suited to this approach, in so far as EMA recognised high levels of unmet medical need to be ‘an important feature since this opens the possibility to use a wider set of regulatory tools and may justify a higher degree of uncertainty at the time of initial authorisation, in contrast to therapeutic areas with authorised treatment options available’.

This raises the question of the distinction between adaptive licensing and CMA, which, it was acknowledged, ‘shared many features’ with the adaptive approach. There are several key differences. First, as EMA’s 2010 strategic document had envisaged, eligibility for CMA is, in principle, more narrowly construed since (as noted in (i) above), it applies only to seriously debilitating or life-threatening conditions, whereas the adaptive approach is, in principle, applicable to most new products. Furthermore, the CMA process, unlike that for adaptive licensing, does not envisage early and ongoing dialogue with multiple stakeholders, notably HTA agencies and payers. Finally, the adaptive approach places stronger emphasis than does CMA on the communication of higher than usual levels of uncertainty to patients and providers of care.

An analysis of the EMA programme thus enables us to delineate a number of characteristics of an adaptive approach to the licensing of pharmaceuticals. These include a non-binary approach to regulatory evaluation of the safety, efficacy and quality of drugs (the ‘magic moment’ of licensing is no longer transformative to the same degree as previously); an iterative approach to evidence generation which entails a trade-off between initially higher levels of uncertainty and earlier access for patients (especially those with unmet clinical needs), coupled with the greater use of data from sources beyond clinical trials; a more holistic approach to drug development with multiple stakeholders being involved throughout rather than only subsequent to the licensing decision; and

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103 EMA (n 101), 2.
104 id.
105 Eichler and others (n 2), 430. See also (n 160) below.
106 Above (n 98) and accompanying text.
107 Eichler and others (n 2), 430.
108 This is reflective of the EU’s limited competence in matters of health, discussed in the next section.
109 Eichler and others (n 2), 430.
110 A number of commentators prefer the term ‘adaptive pathways’ on the bases that the early and ongoing involvement of HTA agencies/payers serves to elide the distinction between licensing and coverage; and that the adaptive approach focuses also on post-licensing matters: see Eichler and others (n 54), 235.
‘potential benefits for companies [of] an earlier revenue stream than under a conventional licensing pathway and less expensive and shorter clinical trials’,\textsuperscript{111} which in turn should stimulate (or, at least, not hinder) innovation on the part of pharmaceutical manufacturers.

(iii) Outcomes of the pilot

EMAs received 62 applications for the pilot, although most did not fulfil the criteria for eligibility: around one-third of these were cancer drugs.\textsuperscript{112} Of these, eighteen progressed to full discussion of the process (in which HTA bodies participated),\textsuperscript{113} but only seven proceeded to the scientific advice stage.\textsuperscript{114}

The Agency’s final evaluation of the project was guarded in tone. It argued that the pilot had demonstrated that multi-stakeholder dialogue could be fostered with a view to early alignment of differing requirements (for example, those imposed by HTA agencies as well as those by EMA), thereby creating a common evidence base which should reduce the prospects of the drug failing to surmount the various hurdles. It also felt that the approach could support medicine development in areas where evidence generation is challenging (such as rare cancers).\textsuperscript{115} However, it acknowledged that ‘adaptive pathways is not a suitable approach for the development of all products’.\textsuperscript{116} This is significant, because earlier indications had been that ambitions for the approach had been much broader: in 2012, Eichler and colleagues had stated that ‘adaptive licensing is envisioned as the ultimate replacement for the current development and authorization process/model, and as such would be applicable to most new products’.\textsuperscript{117}

The EMA’s ambivalent response must be viewed in the light of significant criticism – described in one analysis as ‘outright hostility’\textsuperscript{118} – of the adaptive approach during the lifetime of the pilot: even EMA noted, with some understatement, that ‘stakeholders’ interest has been high’.\textsuperscript{119}

The most prominent critique came in the form of a letter to the Agency from a group of leading scientists, including a past president of the Royal College of Physicians and the Director of the Nordic Cochrane Centre, which questioned a number of assumptions underpinning the pilot,

\begin{itemize}
  \item \textsuperscript{111} Eichler and others (n 2), 431.
  \item \textsuperscript{113} ibid, 12.
  \item \textsuperscript{114} This is where EMA provides advice to developers to ensure that appropriate tests and studies are undertaken to support quality, safety and efficacy: see Reg. 726/2004, (n 51), art. 57(1)(n).
  \item \textsuperscript{115} EMA (n 112), 16-17.
  \item \textsuperscript{116} ibid, 17.
  \item \textsuperscript{117} Eichler and others (n 2), 430.
  \item \textsuperscript{118} ‘EMA Returns to the Fray on Adaptive Pathways’, \textit{Pharmaceutical Executive}, 29 November 2016.
\end{itemize}
including the notion that the current regulatory processes stifled innovation and delayed access to new drugs, and that early market entry was beneficial to society. Another important contribution to the discussion was made by a group of authors employed by payers (health authorities and insurance companies), who, inter alia, ‘saw little need to change’ the approval process given recent stability in rates of authorisation; noted that the inevitable lack of data made decisions on reimbursement of drugs difficult (especially where this was connected to the value of the treatment) and risked generating higher and higher prices as the applicable population was gradually expanded; pointed out the difficulty of withdrawing from the market drugs which were later found to be ineffective; and expressed concern that, ‘due to the inherent uncertainty of earlier access, greater risks to patients are expected to arise from this uncertainty’. They concluded that ‘adaptive pathways cannot be the preferred approach for new medicines in the future’. The influential German HTA agency, the Institute for Quality and Efficiency in Health Care, also identified data limitations as problematic, meaning that ‘robust conclusions on benefit and harm’ could not be drawn, and argued that it was ‘high time to pause for a moment and rethink the whole concept’. Elsewhere, an article in the British Medical Journal suggested that adaptive licensing had been introduced to placate the pharmaceutical industry, a claim which was supported in a joint briefing paper produced by a variety of public health advocacy groups and research institutes, which also argued that the adaptive approach (viewed as ‘paving the way to deregulation’) might lead to ‘premature marketing authorisation’ becoming the norm, ‘therefore putting EU citizens’ health unnecessarily at risk’. Similar points were made by the umbrella body for European consumer

120 Silvio Garattini and others (13 May 2016), available at <https://epha.org/scientists-voice-concerns-about-adaptive-pathways/> (accessed 16 April 2019). The EMA’s response maintained that failure to adapt the current research, authorisation and access path ‘would indeed be bad for those patients who are in urgent need of better treatments’, and reiterated its ‘full agreement’ that ‘adaptive pathways is not meant to apply to all medicines, but only to those likely to offer help for a patient population with an unmet medical need’:


123 Courtney Davis and others, “‘Adaptive pathways” to drug authorisation: adapting to industry?” (2016) 354 BMJ i4437.

124 Health Action International and others, “‘Adaptive licensing” or “adaptive pathways”: Deregulation under the guise of earlier access’, <http://haiweb.org/publication/adaptive-
organisations, which expressed doubts as to the added value of the adaptive process and concluded that it (and other early licensing processes) ‘must remain the exception rather than the rule’.

**Lessons of the EMA experience**

Given the weight of the criticism cited above, it is perhaps unsurprising that the future prospects for adaptive licensing within the EU are now highly unclear. In its final evaluation report, EMA acknowledged it to be a ‘concept in development which will be fine-tuned’; some two years later, the Commissioner for Health and Food Safety acknowledged that the project had subsequently been neglected, with the imminent move of EMA from London post-Brexit presenting another rationale for inattention to it. The view that ‘the drive in Europe toward adaptive pathways today gives every appearance of having run into the sand’ therefore seems to be an accurate summation of the current state of play.

However, while there may be scant signs of further progress in this direction in the EU in the immediate future, the long-term trend towards manufacture of medicines which treat diseases in a more targeted, precise manner than the blockbuster and me-too drugs of the past means that the ‘evidence versus access’ problem presents an ongoing, and seemingly permanent, challenge to pharmaceutical regulators globally. Relatedly, as noted previously, authorisation processes across a number of jurisdictions are increasingly diverging from the traditional model. Against this backdrop of continuing innovation and regulatory evolution, the experiences of the (failed?) EMA pilot can prove highly instructive to those engaged with the licensing of pharmaceuticals, as well as to scholars of regulation in general. The remainder of this article seeks to outline these implications.

Before turning to these, however, it is first worth pausing to note that the developments described in this article provide further evidence of a broader and growing trend towards the ‘Europeanisation of health policy’. This refers to the extension of EU involvement in health beyond licensing or adaptive pathways-deregulation-under-the-guise-of-earlier-access/> (accessed 16 April 2019).


126 EMA (n 112), 22.


128 ibid.

129 See above (nn 3-10) and accompanying text; O’Donnell, ibid.

the focus, rooted in the Treaties, on public health and the impact of the internal market on health services, to matters traditionally within Member State competence, such as financing of health systems. The non-linear, holistic nature of the adaptive approach means that, rather than being clearly divisible into a licensing stage, for which the EU is responsible, followed by a coverage/reimbursement stage, which falls to Member States as a dimension of their regulation of the financing of health systems, the distinction between the processes is blurred. Should the adaptive approach become regularly used (which, at present, seems unlikely) there is potential for a fully shared EMA/HTA regulatory space to emerge, marked not only by formal arrangements for cooperation between institutions, but also by softer modes such as converging discourses, exchange of views and information, learning, and networking.

Focusing more specifically upon regulation, a second notable feature of recent developments in pharmaceutical licensing is that they suggest a modification of the regulatory function. As noted above, given its origins in the thalidomide tragedy, contemporary pharmaceutical regulation places central emphasis on ensuring safety and quality, and EMA’s approach to marketing authorisation has been described as ‘fit[ting] squarely within a standard risk regulation model’. The adaptive approach can feasibly also be described as a form of ‘risk regulation’, but it is of a very different character, reflective of the elasticity of the notion of ‘risk’ which carries connotations which are both negative (the likelihood of harm or loss from a hazard) and positive (‘taking a risk’ being ‘a core element in the creation of a dynamic economy and innovative society’).

As Wirthumer-Hoche and Bloechl-Daum state, the role of drug regulatory agencies to protect public health ‘translates into two distinct objectives: first, into an obligation to protect patients against ineffective or harmful drugs and, second, to protect patients against the consequences of untreated disease’. Thus, while the pharmaceutical licensing process within the EU has, to date, strongly emphasised the first of these goals, the obligation to ensure a ‘high level of human health protection’ under Article 168(1) TFEU can certainly be construed as extending to


131 Compare the parallel consultation procedure between EMA and the European Network for Health Technology Assessment (EUnetHTA), which provides feedback on plans for evidence generation to support decision-making on marketing authorisation and reimbursement at the same time commenced in 2010: see EMA/EUnetHTA, ‘Guidance for parallel consultation’, EMA/410962/2017 (30 June 2017).

132 Hervey and McHale (n 57), 326.

133 David Denney, Risk and Society (Sage 2005) 11. See also Hervey and McHale, ibid, 292-93.

134 Christa Wirthumer-Hoche and Brigitte Bloechl-Daum, ‘Current Issues in Drug Regulation’, in Müller, ed. (n 27), 19.
implementation of measures to enhance access to treatments – especially in areas where alternatives do not exist – since enhancement of access should serve to protect (in fact, will almost certainly enhance) the health of EU citizens. One way of conceptualising this second role is to consider the regulator’s task, rather than being evaluation of the standard (and legally mandated) risk-benefit balance, to lie in assessment of a risk-risk balance: weighing the risk of untreated disease against the risk of the treatment itself (or, expressed somewhat differently, balancing protection and promotion of public health against the principle of ‘first do no harm’). It might also be argued that the regulator is balancing the (positive) risk of encouraging innovation against the (negative) risk that this may prove harmful to patients. In any event, the recent focus on enhancement of access and encouragement of innovation appears to signal a shift in the function of the regulator from one of gatekeeper to one of enabler.

It is this apparent change in regulatory function which has generated much of the opposition to the adaptive approach, suggesting that the form of risk regulation which has historically been exercised by EMA, grounded in protection from harm, continues to enjoy broad support in spite of pressure for earlier access and availability of pharmaceuticals. The concerns voiced by various stakeholders during the period of the pilot can thus be understood as challenges to the legitimacy of the modified regulatory role – that is, to its ‘acceptability and credibility’ – notwithstanding that this role appears consonant with the broad health mandate conferred on the EU by Article 168 TFEU. These challenges can usefully be categorised by reference to the quadripartite model advanced by Black, which divides claims to regulatory legitimacy into those which are justice-based, functional, constitutional and democratic in character.

Concerns as to whether EMA mechanisms for accelerated access to pharmaceuticals based upon limited evidence are adequate to protect patient safety, as well as those which view the agency as having conceded to industry pressure, may be regarded as justice-based in so far as they relate to ‘the values or ends which the organization is pursuing’. Additionally, the emphasis placed upon gathering of post-licensing ‘real world’ data rather than obtaining it by way of pre-

135 See above (n 85).
136 See Eichler and others (n 41), 907-08.
137 Wirthumer-Hoche and Bloechl-Daum (n 134), 19.
138 Julia Black, ‘Constructing and contesting legitimacy and accountability in polycentric regulatory regimes’ (2008) 2 Regulation and Governance 137, 144.
139 Ibid, 145-46.
140 See eg Health Action International and others (n 124), especially at 2-3; BEUC, (n 125).
141 See eg Davis and others (n 123).
142 Black (n 138), 146.
licensing clinical trials may be viewed as contrary to a dignitarian perspective.\textsuperscript{143} Some respondents to the pilot scheme claimed that it treated patients as ‘guinea pigs’ since ‘a medicine’s harm-benefit balance will not be properly assessed prior to the exposure of the general patient population to a new drug’.\textsuperscript{144} Functional challenges to legitimacy relate in part to the agency’s performance – which is as yet difficult to assess, although low numbers for both the adaptive pilot and the CMA process do not favour the regulator – but also to the extent to which the regulator complies with scientific norms.\textsuperscript{145} Here, the disquiet lies with the substitution of what might be labelled as ‘observational data’, which is widely regarded as less reliable for the testing of hypotheses, for the ‘gold standard’ of randomised controlled trials.\textsuperscript{146} This is especially problematic given that the exercise and application of scientific knowledge may be regarded as central to the legitimation of the EU’s approach to the governance of risk in the arena of public health.\textsuperscript{147}

The constitutional and democratic critiques of the legitimacy of a redefined regulatory role for EMA, which relate to compliance with written norms and commitment to democratic principles, can most profitably be discussed together. Opposition in this context centred upon the absence of any initial democratic endorsement of the pilot project and its goals by the governing EU institutions, it being argued that the pilot ‘seems to be a perfect way of circumventing the democratic process by presenting the European Commission, Parliament and Council with a fait accompli’.\textsuperscript{148} Negative comparisons were drawn with the debate upon new pharmacovigilance legislation in 2010, during which a Commission proposal to apply a CMA-style process to embrace all drugs had been rejected by the Council and Parliament.\textsuperscript{149} Criticism was also expressed of a lack of transparency and of

\textsuperscript{143} For the importance of dignity to the establishment of regulatory legitimacy in the context of technological innovation, see Roger Brownsword, Rights, Regulation and the Technological Revolution (OUP 2008) 41-47.
\textsuperscript{144} Health Action International and others (n 124), 6; see also BEUC (n 125), 8.
\textsuperscript{145} Black (n 138), 146.
\textsuperscript{146} See Garratini and others (n 120), Annex A, (8): describing the EMA term ‘real world data’ as a ‘euphemism’; Institute for Quality and Efficiency in Health Care (n 122); Woodcock (n 61), 379.
\textsuperscript{147} See Mark Flear, Governing Public Health: EU Law, Regulation and Biopolitics (Hart Publishing 2015).
\textsuperscript{148} Health Action International and others (n 124), 10. See also European Public Health Alliance, Will fast-tracking new medicines improve affordability? (EPHA, 2016) 3: ‘framing adaptive pathways as a pilot project has prevented and impeded any political scrutiny’; BEUC (n 125), 11.
\textsuperscript{149} Health Action International and others (n 124), 4, 6. The Commission proposal took the form of a requirement for a ‘risk management system’ for all new medicines: see Commission, ‘Strengthening pharmacovigilance to reduce adverse effects of medicines’, MEMO/08/782 (10 December 2008) 3.
opportunities for stakeholder participation during the progress of the pilot.\textsuperscript{150} Although it was noted that the pilot might function as a precursor for a subsequent full legislative review of the licensing process,\textsuperscript{151} the absence of democratic deliberation \textit{at this stage} was justified by EMA on the basis that the adaptive approach could be implemented without the need to further supplement its existing regulatory tools or legal powers.\textsuperscript{152} However, its assumption that management of uncertainty through ongoing evidence collection following the initial licensing decision could be founded upon the pharmacovigilance legislation,\textsuperscript{153} which enables post-marketing evaluation of efficacy in addition to safety, was also called into question by some participants to the debate. They regarded this to be an improper extension of the scope of the legal authority vested in the Agency.\textsuperscript{154}

A case of regulatory disruption?

Although the preceding analysis has sought to identify the \textit{nature} of the various challenges to legitimacy which EMA has confronted in its efforts to evolve adaptive licensing, there remains the underlying question of \textit{why} legitimacy has been so keenly contested that EMA no longer envisages this approach to be appropriate for all new medicines, and is apparently unclear as to its future prospects at all. It is submitted that the concept of disruption, ‘an overarching theme that frames scholarly inquiries about the legal and regulatory enterprise in the face of technological change’,\textsuperscript{155}

\begin{flushleft}
\textsuperscript{150} BEUC (n 125), 9; Health Action International and others (n 124), 7.
\textsuperscript{151} Health Action International and others (n 124), 10.
\textsuperscript{152} EMA (n 101), 4; EMA (n 112), 8. See also the next section of this article.
\textsuperscript{154} Ermsich and others (n 121), 4; Health Action International and others (n 124), 1; Commission, Pharmaceutical Committee, ‘Relation between pharmaceuticals regulatory framework and timely access of medicines to patients: Reflection on difficulties and opportunities’, PHARM 672 (22 October 2014) 2 (reporting Member State disquiet).
\textsuperscript{155} Brownsword, Scotford and Yeung (n 11), 7.
\end{flushleft}
affords a cogent explanation here.

As previously discussed, a central rationale for the adoption of an adaptive approach is to provide a regulatory framework which is more sympathetic to technological innovation in pharmaceuticals, and is especially suited to the challenges (notably, of an evidential nature) presented by ‘precision medicine’. As is well understood, innovation can be disruptive of markets when it departs from and undermines existing products, providing a different set of values, and ultimately replacing them: the superseding of blockbuster and me-too drugs by nichebusters would seem to afford an excellent example of this phenomenon. Additionally, however, innovative technologies can disrupt a regulatory regime. This occurs when ‘the innovation typically falls within a specific agency’s jurisdiction, but does not fit well within the agency’s regulatory schemes that contemplate more established technologies’. In such circumstances, as the innovation ‘disturb[s] the “deep values” upon which the legitimacy of social orders rests and on which accepted legal and regulatory frameworks draw’, significant contestation over regulatory legitimacy may arise.

EMA sought to defuse conflict of this type by retaining familiar processes and principles. Hence, it was at pains to emphasise that the ‘adaptive... approach can be embedded within the existing regulatory framework using available tools and processes’, that (as noted above) it could be exercised through current legislative authority, and that key normative values, such as the need to demonstrate a positive risk-benefit balance, remained intact. However, as the preceding discussion attests, this strategy certainly did not resolve problems of regulatory legitimacy, and very probably exacerbated them. In understating the extent of disruption, EMA opened itself up to particular contestation when stakeholders identified a disjuncture between the ‘business as usual’ discourse and a regulatory approach which differed in important ways from that which was familiar, and which they had been promised would continue. The existence of this divergence tended to engender suspicion and mistrust, manifested most notably in those critiques which viewed the pilot as a sop to the pharmaceutical industry. On this analysis, although regulatory disruption would have generated problems of legitimacy in any event, EMA might have done better to have explicitly


158 Brownsword, Scotford and Yeung (n 11), 7.


160 EMA (n 119), 4. CMA was identified as the most relevant of the existing processes: see EMA (n 112), 8.

161 See above (n 153) and accompanying text.

162 EMA (n 112), 8.

163 See nn 123, 124 and accompanying text.
acknowledged the extent of change entailed by adoption of the adaptive approach. As Brownsword has observed in similar vein, ‘unless the regulators’ purposes are transparent, there can be no meaningful debate about the acceptability of the measures taken’.164

Conclusion

The EMA adaptive licensing pilot provides an instructive illustration of the difficulties entailed in achieving a fit between regulation and innovative technological development – of resolving the challenge of regulatory connection165 – even in circumstances where producers and consumers apparently share common goals in modification of an existing regulatory framework. All forms of claims to regulatory legitimacy remain contested, demonstrating both the resilience of the existing mode of regulation (notwithstanding its perceived deficiencies), and the disruption to the framework caused by innovation. Attempts to minimise contestation through an ostensible maintenance of the regulatory status quo have served instead to worsen it, as stakeholders come to appreciate the disjuncture between the EMA discourse of normalcy and the disruptive reality. In consequence, the future of the modified regulatory framework in the EU stands in considerable jeopardy.

The analysis presented in this article suggests that the optimistic conclusion of Dorbeck-Jung that adaptive licensing represents a ‘promising realistic responsive approach’ now warrants significant modification in light of the EMA experience.166 At present, it appears some distance away from becoming the ‘new paradigm’ for pharmaceutical regulation, which it was suggested might emerge.167 However, given that the ‘evidence versus access’ problem will surely persist, efforts to reform the regulatory framework will continue to prove necessary. Licensing of pharmaceuticals thus seems likely to prove a fruitful area of critical analysis by scholars of the regulation of innovative technologies for some time to come.

164 Brownsword (n 143), 249.
165 For discussion of this challenge, see ibid, chap.6.
166 Bärbel Dorbeck-Jung, ‘Transcending the Myth of Law’s Stifling Technological Innovation: How Adaptive Drug Licensing Processes Are Maintaining Legitimate Regulatory Connections’, in Brownsword, Scotford and Yeung, eds. (n 11), 945. The author does note that ‘only very tentative lessons can be drawn with regard to legitimacy issues’ at the ‘early stage of... implementation’ at which her analysis was conducted: id.