TITLE: From the European Medicines Agency to Project Orbis: New activities and challenges to facilitate UK Oncology Drug Approval following Brexit

Authors:

Mark P. Lythgoe MBBS[1], Jonathan Krell PhD[1], Mark Bower* PhD[2] , Ravindhi Murphy PhD[1,7], John Marriott* PhD[3], Sarah P Blagden* PhD[4], Ajay Aggawal MD PhD[5,6], Richard Sullivan* MD PhD[5]

*indicates Professor

Affiliations:

[1] Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, UK

[2]Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, UK

[3] School of Pharmacy, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[4] Department of Oncology, University of Oxford, Oxford, UK

[5] Institute of Cancer Policy, School of Cancer Sciences, King's College London, London, UK

[6] Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, UK

[7] Drug Development, Cancer Research UK, 2 Redman Place, London, UK

Corresponding Authors:

Mark P. Lythgoe, MBBS
Imperial College London
Hammersmith Hospital Campus
Du Cane Road, London, UK, W12 0HS
(+44) 0208-7589-511
M.Lythgoe@imperial.ac.uk

Word Count: 4994
Tables: 3
Figure: 1

Summary

The departure of the UK from the European Union (EU) and affiliated European regulatory bodies on the 31st December 2020, including the European Medicines Agency, (EMA), has resulted in the Medicines and Healthcare products Regulatory Agency (MHRA) becoming an independent national regulator. This has required a fundamental transformation of the UK drug regulatory landscape, creating both opportunities and challenges for future oncology drug development. New UK pharmaceutical policy has sought to establish the UK as an attractive market for drug development and regulatory review, by offering expedited review pathways coupled to strong collaborative relations with other leading international medicines regulators, outside of Europe. Oncology is a key global therapy area for both drug development and regulatory approval, and the UK government has been keen to demonstrate regulatory innovation and international collaboration in the approval of new cancer medicines. In this review, we examine the new UK regulatory frameworks, policies, and global collaborations affecting new oncology drug approvals following departure from the EU. We explore some of the challenges which may lie ahead as the UK forges ahead with new and independent regulatory review and approval processes for the next generation of cancer medicines.

MANUSCRIPT:

1. INTRODUCTION

The United Kingdom (UK) formally left the European Union (EU) on 31st January 2020 (Brexit). Following a short transition period, ending on 31st December 2020, the UK withdrew from participating EU institutions, including the European Medicines Agency (EMA), leaving the Medicines and Healthcare products Regulatory Agency (MHRA) as the UK's standalone medicine and medical device regulator. The departure from the EU has necessitated significant healthcare reform in the UK. New government policy has consistently focused on transforming the UK into a 'life sciences superpower', capitalising on the UK's strong science base and previous track record in delivering timely innovations (e.g. COVID-19 vaccines)[1,2]. A central tenet of these new policies is establishing the UK as an attractive market for new drug development by forging greater international collaboration, beyond the EU, and offering expedited regulatory review[3]. Effective and efficient medicine regulation by the MHRA is fundamental for realising this ambition, and new oncology drug approvals are at the forefront of this.

All medicine regulation in the UK had been subject to European Law since 1973. However, following the outcome of the EU membership referendum in 2016, the UK has become a designated 'third country' (outside EU and European Economic Community) with EU pharmaceutical law ceasing to apply, except for Northern Ireland (NI) which under the Ireland/Northern Ireland protocol continues under EU jurisdiction [4]. To replace EU pharmaceutical law, the UK has enacted the Medicines and Medical Device (MMD) Act to regulate human medicines, veterinary medicines and medical devices[5]. MMD has provided a crucial step towards forging an independent regulatory landscape and new pharmaceutical policies following Brexit [6].

Decoupling of the MHRA from the EMA infrastructure has presented both significant opportunities and challenges for medicines review in the UK. A key focus of new UK pharmaceutical policy is accelerating regulatory review and drug approval. To enable this, the MHRA has launched multiple new marketing authorization application (MAA)

assessment routes (outlined in **table 1),** and is fostering greater collaboration (see **table 2)** with other international regulators (e.g. Project Orbis) outside the EU to accelerate the regulatory review of new medicines, whilst retaining full independence in all approval decisions[7]. Expedited approval of the next generation of new cancer medicines is viewed as a key pillar of this new policy[8,9]. However, despite the rhetoric around the potential benefits this may afford for cancer patients, significant challenges in terms of ensuring appropriate access and reimbursement remain.

This policy review focuses on new UK medicines regulatory frameworks, global collaborations and policies affecting new oncology drug approvals in place following the departure from the EU. We explore the potential opportunities and challenges of these new frameworks for cancer medicines, as the UK forges ahead with new independent regulatory review and approval processes.

2. Forging Greater International Collaboration

One of the first steps taken by the MHRA following the end of the UK-EU transition period was joining Project Orbis and commencing work-sharing with the ACCESS Consortium (AC) [8,10]. Both collaborations (**table 2**) bring together the most powerful and influential global medicine regulators (e.g., FDA, Health Canada), with the goal of evaluating new drugs concurrently to expedite multi-geographic approval. Project Orbis has a remit limited to oncology therapies, but the AC review can assess marketing authorization applications in any therapeutic area(s), although oncology has been the previously dominant area.

2.1 Project Orbis

This global collaborative program launched by the US Food and Drug Administration (FDA) Oncology Centre of Excellence in May 2019 aims to speed up patient access to new cancer medicines, both in the USA and internationally, through a framework of parallel regulatory submission and review[11,12]. Previously, the FDA would typically

receive new oncology drug applications first, with other national regulators waiting months (or years) before MAAs are submitted[13–16]. To facilitate faster international access, the FDA works alongside other selected regulators in the evaluation of new oncology therapies, permitting a collaborative review. The FDA is the principal partner for all reviews, with evidence that it typically reaches a regulatory decision before other partners, however a central credo remains that each regulator retains full independence regarding regulatory decision-making and is not obliged, in principle, to follow decisions made by other partners[11,17].

Currently there are seven global regulatory Project Orbis partners from the UK, Australia, Canada, Singapore, Switzerland, Brazil and Israel[8,11,12]. Participation of the FDA and at least one other regulatory partner is necessary for review via this pathway. Selection of medicines is determined by the FDA, however, other partners may propose drugs for inclusion. The submission type determines the degree of potential collaboration between the FDA and Project Orbis Partner(s) (**table 2**). Type A (regular Orbis), concurrent or near-concurrent (within 30-days) MAA submission to regulators, and Type B (modified Orbis), delay between 30-days to 3 months of MAA submission between FDA and partner agency, both permit concurrent review, though Type A permits maximal collaboration and the possibility of concurrent regulatory action. Type C (Written report only Orbis) submissions, occurring only after the FDA has taken definitive regulatory action, is restricted to the sharing of completed regulatory documents from the FDA only. New oncology medicines must meet eligibility for the FDA expedited approval program, Priority Review, to be considered for Project Orbis[12]. This framework shortens FDA review time to 6 months from the standard 10 months and is designed for drugs which treat serious conditions and/or offer significant improvement, although not explicitly defined, in effectiveness or safety over existing care[18]. The MHRA specifies that for inclusion in Project Orbis, MAAs must meet the qualifying criteria for the Innovative Licensing and Access Pathway[8].

In the first year of activity (preceding MHRA participation) Project Orbis supported 60 new oncology MAAs, resulting in 38 new oncology therapy approvals across partner

countries[11]. In the first year of MHRA participation, 6 new oncology drugs/indications have been approved in the UK via this pathway, with a similar trend for 2022[17]. The most frequent submission category has been Type B (8 submissions) followed by Type A (7 submissions) and Type C (6 submissions). The first MAA to be approved was the supplementary indication for osimertinib (May 2021) as adjuvant treatment for epidermal growth factor receptor mutated non-small cell lung cancer (NSCLC) [19,20]. The first new drug (initial indication) approved was sotorasib (September 2021) for 2nd line treatment of KRAS G12C-mutated metastatic NSCLC [21]. Both approvals preceded EMA market authorization, and each manufacturer reached agreements with National Health Service (NHS) England to permit patients access prior to formal National Institute for Health and Care Excellence (NICE) review [22,23]. The next UK approval was for sacituzumab govitican in breast cancer, however despite UK regulatory approval, a reimbursement agreement was not initially reached[24]. All new cancer drugs reviewed by Project Orbis were approved by the UK before the EU, by a median of 3 months, but after the FDA had approved them (median 5 month delay).

2.2 ACCESS Consortium

The ACCESS Consortium (AC) predates Project Orbis by 12 years and is a coalition of medium-sized 'like-minded' regulatory authorities working together to '*provide faster access to safe, effective and high-quality medicines'* [25].The original consortium was formed in 2007 and has expanded to include regulators from Australia, Canada, Singapore, Switzerland and the UK, now representing a collective population of 150 million people [25].

The AC is committed to maximising collaboration by aligning regulatory approaches and facilitating simultaneous review to provide more timely access to new medicines, across all therapeutic areas. Echoing Project Orbis, each regulator makes its own decisions and is not bound to those of others[10]. New MAAs must be submitted simultaneously to at least two AC members[26]. Work-sharing concludes at the end of the MAA evaluation phase, as each regulator will progress independently towards making a final determination[10,26]. This

model of work-sharing is being reviewed by other national regulators to see if it is an exemplar for sharing resources across regions.

The AC has been active in supporting the regulatory approval of new cancer medicines, however all pre-date MHRA participation[7,27]. Currently, only one new non-oncology medicine (faricimab) has been approved in the UK via this route. This compares to 11 new cancer drugs/indications approved by Project Orbis, suggesting this latter pathway will be the dominant collaborative route for new cancer drug approvals in the UK[17].

3. Faster Drug Approval Routes

Project Orbis and the ACCESS consortium, reflect new UK policy, accelerated by Brexit, to establish itself as a priority country for new medicine approval for drug developers by offering accelerated routes for regulatory review and market authorization[3]. Initially the MHRA has maintained pre-Brexit levels of regulatory support in key areas, by echoing EMA regulatory practices and putting 'reliance' procedures in place[23]. However, greater focus is now being placed on new regulatory pathways (**Table 1**), such as the Innovative Licensing and Access Pathway, accelerated assessment and rolling reviews, with the goal of achieving faster regulatory review [28–30]. The UK now has a complex, interlocking set of procedures and pathways germane to oncology (reviewed below).

3.1 'Reliance' Procedures

Post-Brexit, the MHRA has developed 'reliance routes' permitting a shortened assessment procedure for new medicines appraised by EU centralised, decentralised, and mutual recognition procedures[31]. In these situations, the MHRA relies on analysis and decisions by the EMA to approve new medicines. Regulatory reliance, a principle supported by the World Health Organisation (WHO) to improve the availability globally of new medicines, between the MHRA and the EMA could significantly mitigate the potential impact of Brexit in the approval of new cancer medicines and beyond. Therefore, the MHRA has put two independent reliance pathways (**table 1**) in place, the EC Decision Reliance Procedure (ECDRP) for drugs approved by central EU review and the Decentralised and Mutual Recognition Reliance Procedure (MRDCRP) for drugs approved in EU member states through decentralised and mutual recognition procedures[31,32].

3.2 Conditional Marketing Authorizations

The MHRA has also introduced a Conditional Marketing Authorisation (CMA) pathway for new drugs[33]. This framework maintains continuity with the EMA framework (**table 1**) of

the same name and is intended for new therapies which address significant 'unmet medical needs', such as serious or life-threatening diseases where no satisfactory treatments exist [34]. Drugs must demonstrate preliminary evidence judged to be 'highly significant', with comprehensive clinical data permitting full regulatory approval not yet available but likely to be soon[33]. CMAs are valid for one-year and renewable annually or when clinical benefit is determined. Parallels have been drawn between CMA and FDA Accelerated Approval (AA) pathways, as both permit earlier regulatory approval on preliminary results and require further confirmatory clinical evidence to be converted to standard approval at a later timepoint[35]. However, there are some notable differences. AA is granted on the basis of effect on a "surrogate end point that is reasonably likely to predict clinical benefit', most typically Overall Response Rate (ORR), whilst CMAs rely on a 'benefit/risk assessment' based on less comprehensive clinical data than normally required, where the benefit of immediate availability outweighs the risk inherent in the fact that additional data is required. CMAs have a narrower focus, being restricted to initial MAAs only, unlike AA which can be used for both initial and supplementary MAAs, partially accounts for higher usage of FDA AA compared to EMA and MHRA CMAs[35]. The first CMA to be granted in the UK was for tepotinib in NSCLC, notably this was also approved by Project Orbis demonstrating the overlapping functionality of different new regulatory pathways.[17].

In parallel the MHRA has maintained the existing EMA scheme for market authorization under 'exceptional circumstances', for a small number of medicines where comprehensive data cannot be provided, because the condition is rare, or collection of information is not possible or unethical[33]. This scheme will maintain the same eligibility criteria as the EMA, considering other regulators decisions, but with the MHRA making the final determination.

3.3 Innovative Licensing and Access Pathway

A new regulatory pathway, called the Innovative Licensing and Access Pathway (ILAP) was launched in January 2021 with the aim of accelerating the time-to-market for

innovative medicines, facilitating earlier patient access[28]. Core design elements were inspired by the success of the Research to Access Pathway for Investigational Drugs for COVID-19 (RAPID C-19), which provided prompt access to life-saving treatments (e.g. tocilizumab) during the pandemic [36]. The ILAP is open to both commercial and non-commercial (e.g. academic) sponsors, and aims to streamline patient access to safe, financially sustainable and innovative medicines, allowing drug developers end-to-end integrated regulatory support, from preclinical development to market authorization (**figure 1**). ILAP designation is uniquely applied to a specific molecule or therapy, rather than an indication, allowing developers an opportunity to glean early regulatory insight into clinical positioning and probable approval success. Criteria (**table 3**) include demonstrating the medicinal product has the 'potential to offer benefits to patients, including proposed improved efficacy and safety, and contribution to patient care or quality of life'. Therefore the ILAP pathway may afford an opportunity to incorporate patient reported outcomes (PROs) and value-based frameworks, such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to help discriminate new medicinal products associated with clinically relevant benefits from those which offer only marginal improvements over existing treatments[37,38] . Furthermore, this pathway features early access to key stakeholders beyond the regulator, including patient advocacy organisation, allowing the 'patient voice' to be embedded in the regulatory process, and health technology assessment (HTA) bodies[28,39]. Earlier engagement of NICE, or other HTA organisation, aims to 'smooth the journey' through clinical trials to the NHS[28].

The first step in the ILAP is developing an 'Innovation Passport' (IP) [28]. Sponsors, particularly at an early stage of drug development, will explore with the MHRA to determine if their Investigational Medicinal Product (IMP) qualifies for ILAP/IP designation. If granted, the developer and MHRA will create a 'Targeted Development Profile (TPD), similar to the WHO 'Target Product Profiles', this will provide a 'product-specific roadmap' with the goal of achieving early regulatory approval and patient access[40,41]. The TDP offers access to specialist toolkits which can be utilised to ensure

development is efficient and 'regulation and access ready'. ILAP designation is also a mandatory stipulation for oncology drugs to be reviewed via Project Orbis[8].

The first ILAP/IP designation was granted to belzutifan in February 2021 for the treatment of Von Hippel-Lindau disease-associated tumours[42]. This received UK market authorization only 15-months later (May 2022), demonstrating how this pathway can expedite approval. Furthermore, belzutifan was also approved via Project Orbis, demonstrating the compatibility, and acceptance, of this pathway by other global regulators[43]. The MHRA does not currently publish information on therapies granted ILAP/IP review status, however reports receiving 5-6 IP applications monthly, with 41 ILAP/IP designations granted out of 71 applications received during 2021[44]. The highest proportion of applications are for new oncology drugs, therefore this pathway is likely to be highly significant for new cancer medicines.

3.4 Other Key Regulatory Review Pathways

Accelerated Assessment; In January 2021, the MHRA developed a new accelerated assessment route offering a 150-day assessment timeline focused on accelerating regulatory approval of new medicines[30]. This program shares similarities with the EMA Accelerated Assessment and FDA Priority Review pathways which also offers a reduced review timeframe[18,45]. However, compared to the EMA pathway, this regulatory route is broader in scope, with less restrictive eligibility, being considered for 'all high-quality new MAAs'[30].

Rolling Review (RR); A new pathway, set up in January 2021, which permits quality, non-clinical or clinical data to be submitted and reviewed in increments as it becomes available. This route is intended to streamline the development of novel medicines by offering periodic regulatory interactions, minimising risk of failure during regulatory assessments. It can be used for any therapy area and can operate independently or synergistically with other regulatory frameworks (e.g. ILAP). Other regulators offer similar

processes, but typically with limited focus. For example, the FDA offers 'Real-Time Oncology Reviews (RTOR)' which facilitates review of new cancer medicines[46].

Early Access to Medicines Scheme (EAMS); This scheme, initially launched in 2014, permits early patient access to IMPs nearing the end of clinical development in areas of high unmet medical need when a major advantage over existing therapies is demonstrated [28,47]. EAMS bridges the gap between an IMP completing positive clinical trials and becoming a UK authorised medicine and differs from the ILAP, which is focused on development (**table 1**) rather than access. EAMS has provided early access to numerous oncology drugs, for example, facilitating access to pembrolizumab for >500 patients with advanced melanoma before regulatory approval. The MHRA has expressed a desire to develop this pathway further, increasing the scope of activity.

3.5 Northern Ireland MHRA Authorised Route

The protocol on Ireland/Northern Ireland forms part of the Brexit agreement that established the UK's withdrawal terms from the EU[48,49]. EU pharmaceutical law now only applies to the UK in respect of NI. This ties NI to EMA regulatory determinations, with the rest of the UK following MHRA decisions. In March 2020, the divergence in regulatory framework became a significant flashpoint in the impact of Brexit on NI, when the MHRA approved osimertinib as adjuvant therapy in NSCLC before the EMA[50]. Highlighting how every time a new drug is approved in the UK, it will not automatically mean it is approved and available for use in NI.

Following discussions between the EU and UK regarding the NI protocol, the European Commission has put forward proposals to stop drug access disparity, particularly around 'innovative life-saving medicines'[51]. It advises adopting a 'bridging solution' that '*will allow any new medicine authorized in the UK to be supplied to Northern Ireland, until the relevant authorisation is also given in the EU*'[52]. The recently introduced 'Northern Ireland MHRA Authorised Route' (NIMAR) should ensure that patients in NI, have access to new medicines at the same time as patients in the rest of the UK, even if not approved by the EMA, in the future[53].

4. Post-Brexit UK Healthcare Policy

New UK government policy is committed to establishing the UK as a 'life sciences superpower' [1,2]. Beyond greater international regulatory collaboration and faster routes for drug approval, new policy seeks to place greater emphasis on the role of patients in UK drug development and regulatory approval, highlighted in the first post-brexit MHRA delivery plan. Furthermore, following the deleterious impact of the COVID-19 pandemic on clinical research, the UK government has enacted new policy to re-ignite this arena, with a focus on driving innovation and collaboration, whilst removing potential red-tape and barriers to research. These new policies will have significant direct and indirect effects on new oncology research and therapy development and are important to consider.

4.1 MHRA Delivery Plan 2021-23

In July 2021, the MHRA published its first post-Brexit delivery plan 'Putting Patients first: a New Era for our Agency (PPF)'[54]. Following the departure from the EU, PPF outlines the agency's goal to '*seize the opportunities to evolve the existing regulatory framework and keep pace with fast-moving life science developments'* [3]. PPF draws on the findings of Baroness Cumberlege's Independent Medicines and Medical Devices safety review, which chronicled the failure of regulators, alongside those of healthcare professionals, to tackle years of patient harm from medical treatments[55]. This report proposed the MHRA "*invite representatives of those who report adverse events (both patients and healthcare professionals) to be involved in evaluating and making decisions on specific safety concerns*". In response, PPF proposes including patients in all key decision-making committees via new regulatory frameworks, and including PROs as a key aspect of clinical trial governance[3,56]. We propose that the MHRA should also build stronger alliances with healthcare professionals directly involved in clinical trial safety reporting, collecting the experiences of patients participating in clinical trials. In oncology this could be achieved easily by building upon partnerships with healthcare professionals within the

Experimental Cancer Medicine Centre (ECMC) network, a Cancer Research UK/National Institute for Health and Care Research (NIHR) funded consortium of academic drug development units.

PPF complements the aims of the UK Government to transform the nation into a 'life sciences superpower' by establishing closer engagement with life science partners, academic and commercial, to develop innovative healthcare products, especially in the early developmental stages (e.g. ILAP). Fulfilling the objectives of PPF could have wide-reaching implications for new oncology therapy development, including overhauling clinical trial design to welcome novel trial designs that support more rapid and efficient patient recruitment. Currently more than one in four cancer trials fail to enrol sufficient participants, with 18% of trials closing with less than half the target number of patients recruited, therefore new strategies are welcome [57]. Additional objectives include use of international partnerships (e.g. Project Orbis) to provide faster access to next generation cancer medicines and incorporating real-world evidence (RWE) to support regulatory applications (e.g. EAMS) [3,10,25,47]. However, to date RWE has failed to deliver on its promise of high quality clinical data reflecting the need to revitalise the whole RWE ecosystem for cancer [58]. PPF is focused on 'prioritising activities that add real value for patients', and for cancer medicines this may include an opportunity to incorporate PROs and value-based frameworks (e.g. ESMO-MCBS) to ensure that newly approved cancer medicines deliver meaningful benefits for patients in terms of overall survival and quality of life[54]. This may also provide a stronger emphasis on embedded socio-economic studies to support pricing, reimbursement and Health Technology Assessment (HTA) determinations, downstream.

4.2 UK Clinical Research Delivery

In March 2021, the UK government published a new policy, 'Saving and Improving Lives: The Future of UK Clinical Research Delivery', describing the vision for clinical research delivery (2022-25) [59]. This aims to provide a 'research reset' after the COVID-19 pandemic. Core themes echo other post-Brexit policies, with a focus on driving

clinical research innovation and collaboration between key stakeholders (patients, healthcare professionals and regulators). This seeks to build on innovations gleaned during the pandemic, such as delivering platform trials (e.g. RECOVERY trial) and, again, focusing on faster clinical trial authorisation. This will also potentially have significant implications for oncology research over the next decade, with a focus on wider participation and engagement, combined with further innovations to reduce the set-up time for new research.

New cancer clinical trials should benefit from a combined application process for both Clinical Trial Authorisation and Research Ethics Council, promising to significantly shorten approval time[60]. Specific focus has been placed on phase 1 oncology trials, with the MHRA working with the ECMC to support faster set-up, targeting a delivery time within 80-days[60]. Furthermore, building on the success of large precision medicine studies, (e.g. National Lung Matrix trial), further emphasis will be placed on the development of large technical complex innovatively designed cancer trials [61,62]. Faster clinical trial set up and the ability to deliver technically challenging trials has the potential to significantly enhance UK clinical cancer research, driving new cancer drug development. However, such changes, in isolation, will not deliver a radical step change without other major issues being addressed; the NHS capacity to conduct cancer research in light of backlogs and human resource deficiencies, a wider cancer research strategy to address the second translational gap (policy, services and systems and implementation science), deliver clinical research in non-pharmaceutical technologies, especially surgery and radiotherapy, and build in socio-economic studies to inform delivery; and finally, a commitment to the principles of affordable, equitable technologies that deliver clinically meaningful benefit.

5. Discussion

Brexit has necessitated a fundamental transformation of the drug regulatory landscape within the UK. As the sole decision-maker for the market authorization of new medicines in the UK (except NI), the MHRA has focused on enhancing the double-

edged sword of innovation, committing to more drug discovery and development, and faster regulatory review. Some existing EU regulatory frameworks have been retained (e.g. CMA), signalling continued regulatory alignment with the EMA in some areas, whilst in others new drug approval frameworks (e.g. ILAP) have been developed focused on accelerating drug development innovation within the UK [28,33,34]. By joining the AC and Project Orbis, the MHRA is reflecting a policy tilt toward greater global regulatory cooperation beyond the EU. The most significant partnership for new cancer drug development is Project Orbis which may signal closer alignment with US cancer pharmaceutical policy[17].

Leaving the infrastructure of the EU and EMA has affected both drug development and clinical trials in the UK. The MHRA has been able to rapidly re-join international partnerships, such as the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Medical Device Innovation Consortium to resume its role in setting global standards for medicines and medical devices regulation and safety [63]. Following Brexit, the EU has implemented new clinical trials regulations, synchronising conduct and reporting across all member countries with the aim of facilitating more pan-EU trials[64]. This change, and the implementation of new UK clinical research policies, will cause a significant divergence in clinical trial harmonisation between the UK-EU, potentially making the conduct of pan-European clinical trials more challenging. For example, the UK no longer has access to the EU clinical trial registry (e.g., EudraCT, and the new EU Clinical Trial Information System (CTIS)), instead providing updates to the WHO registry (ISRCTN), which may limit the UK's ability to partner in pan-European trials[65]. Reduced alignment with the EU will disproportionately affect oncology, being the largest single therapy area for clinical trials, both in Europe and the UK, accounting for over 1 in 4 of all clinical trials[66]. The UK is one of the leading European countries for early phase oncology trials and has been highly successful in cell and gene therapy clinical trials (accounting for 9% of all global advanced therapy medicinal products (ATMP) trials), emerging as a global leader[65,67]. Policy divergence between the EU and UK may significantly disrupt this status. Further, as greater emphasis is placed by global regulators (e.g. FDA), on

the use of 'multi-regional' clinical trials to support oncology approvals, lack of harmonisation with the EU may ultimately affect the UK's ability to participate in key pivotal licensing trials, and steps are required by the UK government and MHRA to maintain the current status to support cross EU-UK clinical trials[68,69]. With the UK poised to '*declare a war on cancer'* through a new ambitious 10-year Cancer plan, akin to the US Cancer Moonshot and the EU Mission on Cancer, synergy could be gained by expanding, rather than reducing, regulatory and research engagement with the EU[70].

The biggest area for global drug development is oncology. In 2021, more new oncology therapies were approved in Europe and the US than the next four largest therapy areas (infectious disease, cardiovascular disease, haematology, and psychiatry) combined[71,72]. The US and EU dominate the global pharmaceutical market, accounting for 46% and 25% respectively of total medicine expenditure[73]. In comparison, the UK accounts for 2.4% of this market, meaning other higher revenue markets could be prioritised by drug developers[1,74]. To prevent this, the UK cannot afford to substantially differentiate regulatory processes, a key point echoed by The Association of the British Pharmaceutical Industry (ABPI)[1]. Collaboration through regulatory partnerships (e.g. Project Orbis), are critical to ensuring the UK remains at the forefront of access to the next generation of cancer therapies. With the global oncology market expected to double in size by 2030, with fastest growth predicted in Europe, the UK should look to forge stronger collaborative links with the EMA, ensuring the UK does not become a 'late launch' or 'no launch market at all' for prospective cancer drug developers[1,74] .

Regulatory alignment through Project Orbis with the FDA, and other partners, is permitting the earlier UK approval of new oncology drugs, frequently before EU authorisation[17]. Despite the benefit of earlier approval, there are other important sequelae to consider. The FDA frequently uses expedited pathways (74% of 2021 approvals), including AA, to approve new cancer therapies, with higher usage compared to the EMA (e.g. CMA). [13,71]. AA has permitted the expedited regulatory authorisation of highly transformative medicines, such as imatinib in chronic myelogenous leukaemia. However,

505 over the past decade the number of new cancer medicines approved via AA has
506 increased sharply, leading to concerns about the lower potential therapeutic value of new
507 drugs approved by this pathway, and the significant delays in the completion of
508 confirmatory studies [76–78]. An important consequence of early drug approval is greater
509 uncertainty regarding clinical benefit and safety, also once drugs are approved by AA,
510 rescinding market authorization can be problematic and delayed[79–81]. A recent study of
511 18 indications for 10 cancer drugs granted AA but failing to meet primary endpoints in
512 post-approval confirmatory trials, have not had regulatory approval rescinded by the
513 FDA[82]. AA is already impacting UK oncology approvals. Tepotinib was approved by the
514 FDA via AA in February 2021, which was followed by MHRA approval via CMA in Sept
515 2021. Regulatory review was coordinated by Project Orbis, demonstrating a willingness
516 from the MHRA to embrace closer alignment with FDA expedited approval pathways, and
517 potentially wider US pharmaceutical policy. However, unlike FDA AA, the CMA framework
518 has a fixed approval expiry of 1-year and requires annual renewal, which should offer a
519 potential safeguard for timely withdrawal should a drug fail to demonstrate meaningful
520 clinical benefit in confirmatory trials[33]. Notably a similar proposal is being considered to
521 reform the FDA AA pathway[81].
522
523 In the UK regulatory approval alone is insufficient to ensure patient access. In England,
524 NICE is responsible for appraising the cost-effectiveness of new medicines to allow
525 access through the NHS. It aims to complete a health technology appraisal (HTA) within
526 90-days of regulatory approval. Project Orbis is significantly accelerating the earlier
527 regulatory approval of new cancer medicines[17]. In the first-year of MHRA participation,
528 new cancer therapies approved by this pathway received market authorization, a median
529 of 99 days earlier than corresponding EU approval. The delay between regulatory
530 approval and NICE opinion was estimated at 262 days, significantly exceeding the 90-
531 day target[17]. When appraising the clinical benefit of newly approved drugs using the
532 ESMO-MCBS, a reproducible validated tool assessing the magnitude of clinical benefit of
533 new cancer therapies, only 50% of drugs were rated as giving ‘substantial benefit’. This
534 suggests new cancer drugs with more marginal value are being approved, likely
535 compounding efforts to perform a HTA within this defined time limit[38]. However, it is

important to consider that value-based frameworks, including the ESMO-MCBS, have only limited application and utility for regulatory authorities (e.g, EMA) when conducting a formal 'benefit-risk' assessment for regulatory approval[17,37,38].Despite the disconnection between regulatory approval and HTA recommendation, most drugs (83%) were accessible by patients shortly after regulatory approval through agreements between manufacturers and NHS England. However, this was not ubiquitous (e.g. sacituzumab govitecan) demonstrating a need for formal processes to ensure that drugs, particularly those prioritised for expedited regulatory review, are readily accessible to patients following approval. The ILAP framework promises to integrate earlier HTA review, which could potentially mitigate this situation. However, this will only be used for selected qualifying drugs, and in the case of belzutifan, the only oncology drug approved thus far by this pathway, NICE recommendation is not expected until May 2023, 365 days after regulatory approval by Project Orbis.

6. Conclusion

The EU and EMA have been integral partners in the development and approval of new UK oncology drugs for over three decades. Following the decision to leave the EU, the UK is now forging new independent medicines policies, focused on fostering greater collaboration and driving innovation in new cancer medicines development. New international collaborations (e.g. Project Orbis) and new regulatory pathways (e.g. ILAP) have the potential to accelerate new cancer drug approval, permitting earlier patient access to cancer medicines. However, as regulatory approval is only one-step towards patient access, greater focus should be placed on reducing the time intervals between MHRA and NICE (or other HTA body) review, as is planned in the ILAP pathway.

Enthusiasm for faster drug development and approval needs to be tempered with the reality that fast-tracking cancer medicines may simply add more medicines into the market which may not necessarily deliver clinically meaningful benefit or value, whilst adding issues of societal affordability and equity. Despite the quest for faster regulatory approval, the main priority of any medicine's regulator is not simply to lower the bar to

market access but to conduct meticulous reviews and approve only medicines deemed safe and effective. This is essential for ensuring the health and safety of cancer patients now and in the future.

Table & Figure Titles:

Search strategy and selection criteria

Medical and healthcare policy articles were indexed from MEDLINE, PubMed, Cochrane, google scholar, EMBASE databases from January 2018 until June 2022. The UK government website, Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), European Commission (EC), and the Food and Drug Administration (FDA) websites were also searched. Used search terms included 'oncology drugs', 'oncology therapies', 'Medicines and Healthcare products Regulatory Agency', 'MHRA', 'European Medicines Agency', 'EMA', 'UK', 'Brexit', 'Project Orbis', 'Access Consortium', 'Innovation Licensing and Access Pathway', 'ILAP', 'osimertinib', 'sortasib', 'sacituzumab govitecan'. Retrieved publications were manually screened for additional relevant references. Only articles available in English were considered for this policy review. Identified articles which did not include any reference to the 'UK', 'MHRA', 'EMA', 'EC' or 'FDA' were excluded from analysis by co-author consensus.

The majority of references included in this policy review were UK national reports, national cancer policies, and MHRA policy reports, all of which are publicly available. Additional references came from internationally relevant articles, including EC, EMA and WHO policy reports and position statements, also publicly available. Related articles, identified by searches of cancer-related journals (e.g., The Lancet Oncology), and articles published from the regional professional societies, such as the European Society of Medical Oncology (ESMO) were also included. The final reference list was selected on the basis of relevancy for this policy review with agreement of all co-authors.

Acknowledgements

The authors would like to thank Professor Aaron Kesselheim (PORTAL, Harvard University) for his invaluable critical feedback in the evaluation of this manuscript. Dr

Lythgoe would also like to thank the British National Formulary (BNF) Committee and the MHRA Project Orbis for providing clarification in some of the data acquisition.

Conflicts of Interest

MPL, RS, JK, RM and JM have no declarations. AA declares (unrelated) research funding from the National Institute of Health. MB declares honoraria for lectures (unrelated) from Merck, GlaxoSmithKline, Kite Gilead, EUSA pharma. SB declares research grants (unrelated) from Nucana Plc, Astex, Nurix, Tesaro, Redx, MSD, UCB, Sarah Cannon, consulting fees (unrelated) from Ellipses, Amphista, RApportss, Theolytics, honoraria for lectures (unrelated) from Science Museum London, Cheltenham Science Festival, advisory board fees (unrelated) from UCB, Theolytics, Immunocore, and leadership (unrelated) of the LARP society.

Contributions

Conceptualisation - MPL, JK, RS

Literature Search - MPL, JK, RS, SB

Policy Analysis - All authors

Writing - MPL, SB, AA, RS, SB

Critical Feedback - All authors (acknowledgement to Professor Aaron Kesslheim (Harvard University)

REFERENCES

1 ABPI Vision Paper: UK medicines regulatory policy and global influence in a post-pandemic world. https://www.abpi.org.uk/publications/abpi-vision-paper-uk-medicines-regulatory-policy-and-global-influence-in-a-post-pandemic-world/ (accessed Aug 16, 2022).

2 Transforming the UK into a life sciences superpower - GOV.UK. https://www.gov.uk/government/speeches/transforming-the-uk-into-a-life-sciences-superpower (accessed Aug 16, 2022).

3 The Medicines and Healthcare products Regulatory Agency Delivery Plan 2021-2023 - GOV.UK. https://www.gov.uk/government/publications/the-medicines-and-healthcare-products-regulatory-agency-delivery-plan-2021-2023 (accessed Feb 17, 2022).

4 Brexit: the United Kingdom's withdrawal from the European Union | European Medicines Agency. https://www.ema.europa.eu/en/about-us/history-ema/brexit-united-kingdoms-withdrawal-european-union (accessed Feb 16, 2022).

5 Medicines and Medical Devices Act 2021. .

6 Medicines and Medical Devices Act 2021 Assessment - GOV.UK. https://www.gov.uk/government/consultations/consultation-on-the-future-regulation-of-medical-devices-in-the-united-kingdom/medicines-and-medical-devices-act-2021-assessment (accessed Feb 16, 2022).

7 Cutting-edge treatments to be fast-tracked to patients through international collaborations - GOV.UK. https://www.gov.uk/government/news/cutting-edge-treatments-to-be-fast-tracked-to-patients-through-international-collaborations (accessed Feb 17, 2022).

8 Guidance on Project Orbis - GOV.UK. https://www.gov.uk/guidance/guidance-on-project-orbis (accessed Feb 17, 2022).

9 Covid-19 Update: 5 Oct 2020: House of Commons debates - TheyWorkForYou. https://www.theyworkforyou.com/debates/?id=2020-10-05b.625.0 (accessed Feb 17, 2022).

10 Access Consortium - GOV.UK. https://www.gov.uk/guidance/access-consortium (accessed Feb 17, 2022).

11 de Claro RA, Spillman D, Hotaki LT, *et al.* Project orbis: Global collaborative review program. *Clinical Cancer Research* 2020; **26**: 6412–6.

12 Project Orbis | FDA. https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis (accessed Feb 17, 2022).

13 Lythgoe MP, Desai A, Gyawali B, *et al.* Cancer Therapy Approval Timings, Review Speed, and Publication of Pivotal Registration Trials in the US and Europe, 2010-2019. *JAMA Netw Open* 2022; **5**: e2216183–e2216183.

14 Project Orbis: Strengthening International Collaboration for Oncology Product Reviews, Faster Patient Access to Innovative Therapies | FDA. https://www.fda.gov/news-events/fda-voices/project-orbis-strengthening-international-collaboration-oncology-product-reviews-faster-patient (accessed Aug 16, 2022).

15 Downing NS, Zhang AD, Ross JS. Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011–2015. *New England Journal of Medicine* 2017; **376**: 1386–7.

16 Lythgoe M, Krell J, Warner JL, Desai A, Khaki AR. Time intervals between U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) new cancer therapy approvals. *https://doi.org/101200/JCO20213915_suppl1575* 2021; **39**: 1575–1575.

17 Lythgoe MP, Sullivan R. Project Orbis: the UK experience after 1 year. *Lancet Oncol* 2022; **23**: 978–81.
18 Priority Review | FDA. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review (accessed Feb 17, 2022).
19 UK medicines regulator issues its first authorisation under Project Orbis - GOV.UK. https://www.gov.uk/government/news/uk-medicines-regulator-issues-its-first-authorisation-under-project-orbis (accessed Feb 17, 2022).
20 UK medicines regulator issues its first authorisation under Project Orbis - GOV.UK. https://www.gov.uk/government/news/uk-medicines-regulator-issues-its-first-authorisation-under-project-orbis (accessed Feb 16, 2022).
21 NHS England » Lung cancer patients to get breakthrough drug on NHS. https://www.england.nhs.uk/2021/09/lung-cancer-patients-to-get-breakthrough-drug-on-nhs/ (accessed Feb 17, 2022).
22 NHS England » NHS to offer new drug that halves the risk of cancer returning. https://www.england.nhs.uk/2021/05/nhs-to-offer-new-drug-that-halves-the-risk-of-cancer-returning/ (accessed Feb 22, 2022).
23 NHS England » Lung cancer patients to get breakthrough drug on NHS. https://www.england.nhs.uk/2021/09/lung-cancer-patients-to-get-breakthrough-drug-on-nhs/ (accessed Feb 22, 2022).
24 Triple negative incurable breast cancer patients denied extra time with loved ones as drug company fails to reach agreement to secure immediate access to new treatment | Breast Cancer Now. https://breastcancernow.org/about-us/media/press-releases/triple-negative-incurable-breast-cancer-patients-denied-extra-time-loved-ones-drug-company-fails-reach-agreement-secure-immediate-access-new-treatment (accessed Feb 17, 2022).
25 Consortium A. Access Consortium - Strategic Plan 2021-2024. .
26 Access New Active Substance and Biosimilar Work Sharing Initiatives - GOV.UK. https://www.gov.uk/guidance/access-new-active-substance-nas-work-sharing-initiative (accessed Feb 17, 2022).
27 New drug approvals in six major authorities 2011-2020: Focus on Facilitated Regulatory Pathways and Worksharing. 2021.
28 Innovative Licensing and Access Pathway - GOV.UK. https://www.gov.uk/guidance/innovative-licensing-and-access-pathway (accessed Feb 22, 2022).
29 Rolling review for marketing authorisation applications - GOV.UK. https://www.gov.uk/guidance/rolling-review-for-marketing-authorisation-applications (accessed Feb 22, 2022).
30 150-day assessment for national applications for medicines - GOV.UK. https://www.gov.uk/guidance/guidance-on-150-day-assessment-for-national-applications-for-medicines (accessed Feb 22, 2022).
31 European Commission (EC) Decision Reliance Procedure - GOV.UK. https://www.gov.uk/guidance/european-commission-ec-decision-reliance-procedure (accessed Feb 17, 2022).
32 Guidance on the handling of applications for Centrally Authorised Products (CAPs) - GOV.UK. https://www.gov.uk/guidance/guidance-on-the-handling-of-applications-for-centrally-authorised-products-caps (accessed Feb 22, 2022).

33 Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice - GOV.UK. https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice (accessed Feb 22, 2022).
34 Conditional marketing authorisation | European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (accessed Feb 22, 2022).
35 Mehta GU, Claro RA de, Pazdur R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. *JAMA Oncol* 2022; published online Jan 20. DOI:10.1001/JAMAONCOL.2021.6854.
36 Research to access pathway for investigational drugs for COVID-19 (RAPID C-19) | NICE. https://www.nice.org.uk/covid-19/rapid-c19 (accessed Aug 9, 2022).
37 Pignatti F, Wilking U, Postmus D, Wilking N, Delgado J, Bergh J. The value of anticancer drugs — a regulatory view. *Nature Reviews Clinical Oncology 2021 19:3* 2021; **19**: 207–15.
38 Cherny NI, Dafni U, Bogaerts J, *et al.* ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 2017; **28**: 2340–66.
39 NICE collaboration on streamlined licensing and patient access process for new medicines opened on January 1st | News and features | News | NICE. https://www.nice.org.uk/news/article/nice-collaboration-on-streamlined-licensing-and-patient-access-process-for-new-medicines-opened-on-january-1st (accessed Feb 22, 2022).
40 The Target Development Profile Toolkit - GOV.UK. https://www.gov.uk/guidance/the-target-development-profile-toolkit (accessed Feb 22, 2022).
41 WHO target product profiles. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles (accessed Feb 22, 2022).
42 First Innovation Passport awarded to help support development and access to cutting-edge medicines - GOV.UK. https://www.gov.uk/government/news/first-innovation-passport-awarded-to-help-support-development-and-access-to-cutting-edge-medicines (accessed Feb 22, 2022).
43 Project Orbis - GOV.UK. https://www.gov.uk/guidance/guidance-on-project-orbis (accessed April 20, 2022).
44 UK Regulator Issues 41 'Innovation Passports' In First Year Of New Pathway :: Pink Sheet. https://pink.pharmaintelligence.informa.com/PS145471/UK-Regulator-Issues-41-Innovation-Passports-In-First-Year-Of-New-Pathway (accessed Feb 22, 2022).
45 Accelerated assessment | European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment (accessed Feb 22, 2022).
46 Feng C, Virparia R, Mui ETK. Analysis of the Real-Time Oncology Review (RTOR) Pilot Program for Approvals of New Molecular Entities. *Ther Innov Regul Sci* 2021; **55**: 1.
47 Apply for the early access to medicines scheme (EAMS) - GOV.UK. https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams (accessed Aug 16, 2022).

48 Brexit-related guidance for companies | European Medicines Agency. https://www.ema.europa.eu/en/about-us/brexit-uk-withdrawal-eu/brexit-related-guidance-companies (accessed Feb 22, 2022).
49 EU Exit - Frequently Asked Questions | Department of Health. https://www.health-ni.gov.uk/eu-exit-frequently-asked-questions (accessed Feb 22, 2022).
50 NI Protocol preventing approval of life-saving cancer treatment - BelfastTelegraph.co.uk. https://www.belfasttelegraph.co.uk/news/northern-ireland/ni-protocol-preventing-approval-of-life-saving-cancer-treatment-40426159.html (accessed Feb 22, 2022).
51 Brexit: NI will get medicine at same time as GB, EU proposes - BBC News. https://www.bbc.co.uk/news/uk-northern-ireland-59697668 (accessed Feb 22, 2022).
52 EU-UK relations: Commission proposes solution. https://ec.europa.eu/commission/presscorner/detail/en/ip_21_6911 (accessed Feb 22, 2022).
53 The Northern Ireland MHRA Authorised Route (NIMAR) - GOV.UK. https://www.gov.uk/government/publications/the-northern-ireland-mhra-authorised-route-nimar/the-northern-ireland-mhra-authorised-route-nimar (accessed Aug 23, 2022).
54 The Medicines and Healthcare products Regulatory Agency Delivery Plan 2021-2023 - GOV.UK. https://www.gov.uk/government/publications/the-medicines-and-healthcare-products-regulatory-agency-delivery-plan-2021-2023 (accessed Aug 16, 2022).
55 the Independent Medicines and Medical Devices safety Review. https://www.immdsreview.org.uk/ (accessed Feb 22, 2022).
56 Naci H, Forrest R, Davis C. Putting patients first in medicines regulation? *BMJ* 2021; **375**. DOI:10.1136/BMJ.N2883.
57 Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemp Clin Trials Commun* 2018; **11**: 156.
58 Boyle JM, Hegarty G, Frampton C, *et al.* Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study. *Eur J Cancer* 2021; **155**: 136–44.
59 Saving and Improving Lives: The Future of UK Clinical Research Delivery - GOV.UK. https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery/saving-and-improving-lives-the-future-of-uk-clinical-research-delivery (accessed Aug 9, 2022).
60 The Future of Clinical Research Delivery: 2022 to 2025 implementation plan - GOV.UK. https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery-2022-to-2025-implementation-plan/the-future-of-clinical-research-delivery-2022-to-2025-implementation-plan (accessed Aug 9, 2022).
61 Blagden SP, Billingham L, Brown LC, *et al.* Effective delivery of Complex Innovative Design (CID) cancer trials—A consensus statement. *British Journal of Cancer 2020 122:4* 2020; **122**: 473–82.
62 Middleton G, Fletcher P, Popat S, *et al.* The National Lung Matrix Trial of personalized therapy in lung cancer. *Nature 2020 583:7818* 2020; **583**: 807–12.
63 MHRA joins international partnerships to set global standards for medicines and medical devices regulation - GOV.UK. https://www.gov.uk/government/news/mhra-joins-international-partnerships-to-set-global-standards-for-medicines-and-medical-devices-regulation--2 (accessed Oct 27, 2022).

64 Clinical Trials Regulation | European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation (accessed Aug 16, 2022).
65 The past, the present, and the future of clinical trials transparency in the UK - MedRegs. https://medregs.blog.gov.uk/2021/12/22/the-past-the-present-and-the-future-of-clinical-trials-transparency-in-the-uk/ (accessed Aug 16, 2022).
66 Clinical trials landscape UK: GlobalData review january to december 2019. https://www.clinicaltrialsarena.com/comment/overview-of-industry-sponsored-clinical-trials-in-the-uk-2019/ (accessed Feb 22, 2022).
67 Advanced Therapy Treatment Centres network's Industry Advisory Group. National Cell and Gene Therapy Vision for the UK. https://www.theattcnetwork.co.uk/published-material#:~:text=Mar%202022%20%C2%B7%20PDF-,National%20Cell%20and%20Gene%20Therapy%20Vision%20for%20the%20UK,-Mar%202022%20%C2%B7%20PDF (accessed Oct 25, 2022).
68 Singh H, Pazdur R. Importing oncology trials from China: a bridge over troubled waters? *Lancet Oncol* 2022; **0**. DOI:10.1016/S1470-2045(22)00071-7.
69 Benjamin DJ, Prasad V, Lythgoe MP. FDA decisions on new oncological drugs. *Lancet Oncol* 2022; **23**: 585–6.
70 Health and Social Care Secretary to launch new 10-year 'national war on cancer' - GOV.UK. https://www.gov.uk/government/news/health-and-social-care-secretary-to-launch-new-10-year-national-war-on-cancer (accessed Aug 13, 2022).
71 Mullard A. 2021 FDA approvals. *Nat Rev Drug Discov* 2022; **21**: 83–8.
72 Medicines Agency E. Human Medicines Highlights 2021. 2021.
73 • Top pharma markets by country market share 2020 | Statista. https://www.statista.com/statistics/245473/market-share-of-the-leading-10-global-pharmaceutical-markets/ (accessed Aug 16, 2022).
74 Oncology Market Size, Share, Growth, Trends, Report 2021-2030. https://www.precedenceresearch.com/oncology-market (accessed Aug 9, 2022).
75 Accelerated Approval Program | FDA. https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program (accessed Feb 22, 2022).
76 Lythgoe MP, Prasad V. How the US Food and Drug Administration's approval of aducanumab for Alzheimer's disease has implication for oncology and beyond. *Eur J Cancer* 2021; **157**: 68–70.
77 Hwang TJ, Trinh QD, Tibau A, Vokinger KN. Reforms to accelerated approval of new medicines: long overdue. *The Lancet* 2022; **400**: 357–8.
78 Vokinger KN, Kesselheim AS, Glaus CEG, Hwang TJ. Therapeutic Value of Drugs Granted Accelerated Approval or Conditional Marketing Authorization in the US and Europe From 2007 to 2021. *JAMA Health Forum* 2022; **3**: e222685–e222685.
79 Powell K, Lythgoe MP, Prasad V. The Oncologic Drugs Advisory Committee Votes of April 2021—Implications for the Fate of Accelerated Approval. *JAMA Oncol* 2021; published online July 8. DOI:10.1001/JAMAONCOL.2021.3046.
80 Beaver JA, Pazdur R. "Dangling" Accelerated Approvals in Oncology. *New England Journal of Medicine* 2021; **384**: e68.
81 Sachs RE, Donohue JM, Dusetzina SB. Accelerated Approval — Taking the FDA's Concerns Seriously. *https://doi.org/101056/NEJMp2204487* 2022; **387**: 199–201.

82 Gyawali B, Rome BN, Kesselheim AS. Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. *BMJ* 2021; **374**: 1959.
83 The UK Innovative Licensing and Access Pathway—A new paradigm in market access | Xcenda. https://www.xcenda.com/insights/htaq-spring-2022-uk-innovative-licensing-and-access-pathway (accessed Feb 25, 2022).